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PANEL DISCUSSION ON PROPER NUTRITION FOR THE OLDER AGE GROUP*

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MODERATOR MCCAY: As a result of current interest in the relation of fats to cardiovascular disease, there has developed new interest in nutrition on the part of the public. One thing that they ask for is tables of food values. A number of good tables are available. Dr. Jolliffe's book contains some good ones. The one that I like best for public use is issued by the Superintendent of Documents. It costs from 3 to 5 cents, depending upon the number of copies purchased at one time. I brought it along in case any of you are receiving requests for information as to how much fat is in this or that cheese, and the food values in common portions.

Our daily mail contains many questions. The panelists will be able to answer many of them. They also will raise many more.

A letter from last week contains a question with regard to the present extensive use of nitrofuran. It says: "Since an occasional report of the development of neuritic symptoms after nitrofuran administration has been received, this makes the study of vitamin B_1 in relation to it very important. Considering the large number of patients receiving nitrofuran, the incidence of such symptoms is remarkably low, and suggests a possible dietary insufficiency."

The writer of this letter inquires also as to the amount of vitamin B_1 in the diets of some of the foreign nations.

We, in nutrition, cannot answer that type of letter. These questions are of the most interest to the clinical nutritionists.

I was intrigued this morning by the discussion about the formation of stones—

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especially in the bladder and kidneys. I listened especially to that because a Thailand physician is working with us for a Ph.D. degree in nutrition. He is able, consistently, to produce stones in the kidneys and bladders of rats by the use of the old Sippy diet. This may be of no practical use today, but it is apparent that this diet must modify the basic mucoprotein. His findings are of interest, because there have been claims in the clinical literature that the changes caused by the Sippy diet can be reversed. He has found no evidence that they can.

That raises the question about calcium phosphate stones in the kidney and bladder. By our technic, anyone wanting to study them can produce them consistently. They occur in practically every rat ingesting the Sippy diet, which consists of milk treated with sodium bicarbonate. Strangely enough, this does not occur in the hamster.

Another question asked constantly in this age of tranquilizers by people who have been receiving low-salt diets for hypertension is: "I have been told that, now that I am taking tranquilizing drugs, I can eat more salt." Is this an age when people are going to be able to do so?

During my lifetime in nutrition—thirty years—we have constantly received questions about constipation. I am always amazed, because I see no reason for its existence, although I am sure you do. As a nutritionist, I wonder why, with all the knowledge about the use of foods, fruits, and whole-grain breads, we should receive questions about constipation.

We receive many questions about vitamin E and muscular degeneration. This morning, I also was thinking about vitamin E and going back to some of the questions about changing the quality of butterfat. With all the attention now given to fat, it is of interest that long ago we found we could change the quality of butterfat. It could be made much more unsaturated if the cow were fed cod liver oil, for instance. However, when that was done, the cow would later drop dead because of degeneration of the heart muscle. Death seemed to be partly due to a surplus of calories, so I tried to think what could be done to change the butterfat and still not have the cow drop dead with heart lesions from muscle degeneration caused by feeding it a product like cod liver oil.

We receive many questions about arthritis. They are probably largely generated by the tremendous sale of the book "Arthritis and Common Sense." It seemed to make the public interested in nutrition. We have no answers about arthritis. There is nothing in the experimental literature. We say that we know nothing about the diets in that book and their relation to arthritis. Still, the half million copies sold have created a great interest on the part of the public in milk, cod liver oil, warm milk, and various things about which we have no clean-cut answers.

This morning we were talking about stilbestrol. I was thinking back again of the amount that we already have in our diet. As you know, at the time we started feeding stilbestrol to steers on a vast scale (two or three years ago) we also began to receive reports of sterility in mouse colonies throughout the country. That has been one of the big problems. We have been working with the New York State Public Health Service—one of the big producers of mice in the State of New

York—and recently sent a paper to press. We decided that the way to eliminate stilbestrol from the diet of the mice was to eliminate meat scrap. We now plan to use a diet free of meat scrap. This occurrence raised the whole question of how much stilbestrol the public receives. There is no precise answer as far as I know, but may be some of the men here have information on this point.

As I thought when Dr. Jolliffe came in this morning, we ought to have some "fat sparks" in this program, because there is so much interest on the part of the public in fats. Although it has been wholesome to observe this new interest in fats, I have been told that the public does not know our terminology. People—even well educated people—are constantly asking, "What is hydrogenation?" I have tried to formulate a simple explanation of the way to hydrogenate a fat. If it is placed with a catalyst, heated, and hydrogen blown in, the double bonds in the unsaturated fatty acids become partly filled.

The public has come to have an interest not only in the level of fat but in the chemistry of fat, which pleases us very much. So, questions come in constantly, such as: "What will happen to the dairy industry?" "What about the quality of fats?" Questions are asked about fish oil. Some ask about the level of fat.

Then, we receive questions constantly about the heat treatment of fats. We have long known that reports in the literature show that in preparing foods like potato chips, some of the fats in the course of heating reach a temperature as high as 1,000 degrees Fahrenheit before they are diffused out. From 10 to 20 papers discuss experimental cancer in the stomachs of rats following the use of highly heated fats in the diet. I had a seminar on it not long ago and found about that many reports.

We are receiving more and more questions, not only about hydrogenated fats—and they are the only kind that can be used in this high-temperature fat cookery—but about the effect of prolonged heating on fats. What does prolonged or repeated heating do to fat in doughnut machines, where it may be dumped only every week or two? Or to the fat used in French frying in the restaurants? The questions today are not only about the quality and level of fats, but about the effect of heating.

We always receive reverberations. You probably noticed in the *British Medical Journal* or *Lancet* sometime last year, a discussion about corn oil. Some physician facetiously said that, since cardiovascular diseases were less common among conductors than among motormen, he presumed they did not share their corn cake with each other. That facetious remark indicated that he did not think nutrition had much to do with cardiovascular disease.

Dr. Jolliffe, not long ago, stated that the fish-eating habits in Scandinavia probably helped to protect the people. Someone later asked me about bicycle riding by the Scandinavians—they not only eat fish, but they ride bicycles.

These are some of the questions about nutrition contained in the 5 or 10 letters that arrive at our desk each day.

We have not planned our discussion. Each man is free to discuss any questions he wishes. With Dr. Jolliffe near at hand, we shall start with him. Dr. Jolliffe.

DR. JOLLIFFE: Would you like me to talk about reducing, or on the question of fat?

MODERATOR MCCAY: I suggest that you take up what you think is most important.

DR. JOLLIFFE: Probably the most important subject in nutrition in America today is the quality and quantity of fat in our diets and its relation to blood cholesterol and atherogenesis. It is the most important dietary subject in the press. Judging from the letters that we receive—1,500 to 2,500 a month—it is one of the subjects uppermost in the minds of the American public.

In the first place, we must realize that certain points are proved, I think, beyond a reasonable doubt, even though some people still question them.

The first point in my mind is that population groups, or communities, with low blood cholesterol levels have low rates of death from coronary occlusion and myocardial infarction. The reverse is also true. Population groups and communities that have high levels of total blood cholesterol have high rates of coronary occlusion. As far as I know, there is no exception to that finding. It does not apply to the individual but to population groups.

The next point that I think is proved beyond doubt is that one's diet influences the level of blood cholesterol. In experimental animals, every method that has produced atherosclerosis has done so by a similar, or a coincidental, increase in the concentration of blood cholesterol.

The dietary factors that influence the blood cholesterol level include fat (quantity and quality), pyridoxine, the total calories, protein, and possibly the type of carbohydrate eaten.

Two of the outstanding factors that control the level of blood cholesterol are the amount and quality of the fat that goes into the diet. This idea arose about 1951 or 1952 with Laurance Kinsell and his group in Oakland, California. Then it was proved in many other laboratories that certain vegetable oils, when given in large amounts, depress the concentration of blood cholesterol in a hypercholesterolemic subject.

One thing that has not been proved is the mechanism of this action. Neither has it been proved whether or not lowering the blood cholesterol level by dietary means in this type of population (cholesterolemic at age 40 or 50 on the average) will change the rate or the development of coronary artery disease. Nor are the influences of many of the other factors in the diet known.

To people who say, "Factors other than fat influence the cholesterol level—and therefore atherogenesis," I answer "Of course they do." Total calories influence it. Exercise influences it. Hormones influence it. Possibly the anatomic structure of the coronary arteries influence it. Protein influences it.

It is similar to smoking in bed. Smoking in bed is one of the common causes of fire. There are other causes of fire—defective electrical wiring, and what not—but that is no reason to say that it is foolish not to give up smoking in bed, especially after one has had two to three drinks and is alone. That would certainly not be true.

A similar analogy can be made with regard to the quality and type of fat in the diet. One would not be prudent to ignore these warnings.

This is probably enough to provoke some violent dissension.

MODERATOR McCAY: We are receiving questions. We have the start of an interesting collection and hope that we shall have many more so that we can have an open discussion.

Perhaps we should proceed with one of the other members of the group. A journal that we have appreciated very much in recent years is *The American Journal of Clinical Nutrition*. The editor of this much needed journal is Dr. S. O. Waife. I will call next on Dr. Waife from the University of Indiana. Dr. Waife.

DR. WAIFE: I agree with much that Dr. Jolliffe said, but I should like to bring up one point before there is any further discussion of fat-atherosclerosis relationships and other topics in nutrition.

It is important to keep in mind that any subject in the field of nutrition, even any topic in clinical nutrition, has 3 aspects that are not common with other branches of medicine. One is that almost invariably emotional and social factors are involved. Not everyone has cancer, but everyone eats and has fixed ideas as to what is and is not proper. This is based upon generations of time, upon familial and social levels, and upon foods. As you well know, some foods, at least, have emotional significance to people. Interesting differences exist in food preferences between men and women in this country. This shows that foods mean different things to different people. Therefore, in any discussion, we should remember that these factors are backgrounds to our thinking.

Clinical nutrition—that is, studies conducted in man under the best controlled circumstances—present extremely difficult problems. Most nutritional diseases have the disadvantage of taking years, or at least long periods of time, to develop. Changes may occur very slowly and be hard to measure. Thus, we must do a great deal of interpolating from the data on animals. Because of species differences, we should hesitate before we come to conclusions. Often, the conclusions which we jump to, prove to be false. Nevertheless, it is important to keep in mind that, unavoidably, short-term experiments have certain disadvantages, and we cannot say: "therefore, such and such exists."

The most discouraging thing at the moment is that very little factual information is available about nutritional studies in human beings. The amount of good research in clinical nutrition is particularly small. It is growing rapidly, I am happy to say, but we really have few facts upon which to base our information.

I should like to emphasize an important fact that Dr. Jolliffe brought up. I think that we definitely can say that a relationship exists between diets and the blood cholesterol level. There is also a relationship between the blood cholesterol level and the group-incidence of atherosclerosis. Thus there is a relation of A to B, and B to C. The relation of A to C (that is, the jump from diets to atherosclerosis) is something else again, and becomes hazardous.

Underlying our thinking in the statement that the blood cholesterol level and atherosclerosis are related, is an unconscious hope that there is a causal relationship, and that if we could change one, we would be able to alter the other. The evidence for this is insufficient at the moment.

We are dealing with research concerning the way in which diet changes the blood cholesterol level, on the assumption that by doing this we are affecting one

of the mechanisms, or one of the pathogenic processes, in the development of atherosclerosis.

Another point is mentioned in the literature, but not often appreciated. When studies on atherosclerosis are performed in one group of people (be they subjected to diet, or drug therapy, or whatever) with another group kept as a control, or when patients beyond a certain age are compared with younger patients (in the United States, at least), a difficult situation arises, in that we do not know how much atherosclerosis is present in the control group; there is probably a significant amount.

Such studies involve additional complications. Suppose one saw numerous large ulcerations over atheromatous plaques in a 4-plus atherosclerotic aorta, and had to compare the condition with a very small plaque and a developing thrombus in a branch of the coronary artery. The condition of the aorta might be compatible with a long life, despite extensive disease. How can this aortic state be compared with a disease that is not extensive in terms of mass, but happens to be situated in a critical spot? In a comparative study of dietary intakes between patients with coronary artery disease and those without coronary artery disease, one might very well come across a patient who happened to have the lesion in a critical spot, but a very small one in terms of extent, as compared with an extensively diseased aorta.

Although small atherosclerotic lesions may be found at puberty (in rare cases, earlier) and are often found in young adults who have died suddenly, the disease usually takes a long time to develop. It may take a long time to recede. Therefore, even if it could be shown that a dietary change can alter atherosclerotic lesions by modifying cholesterol metabolism or by some other mechanism, we have to look ahead and say that this may mean years of dietary change. One may not be able to do much for the patients within this crucial period o time.

We do not know at the moment whether reversing the blood cholesterfol level has an effect upon atherosclerosis. We do not know whether dietary changes will reverse the disease and, if they do reverse it, for how long the altered diet must be continued.

MODERATOR MCCAY: Thank you, Dr. Waife. We appreciate the importance of the pathologist in this picture. As we look in Cowdry's text on atherosclerosis and read the history of our interest in cholesterol, we know that it goes back to about 1912 in Russia. From a picture by the British medical group visiting Russia recently, we note the same investigator is still working on it. Anyone who survived the revolutions of Russia and has been working on the problem since 1912 must be a pathologist with very good arteries himself.

In our discussion, we have to rely heavily upon the pathologist for such information as whether or not rabbit cholesterol and rabbit atherosclerosis are the same, and likewise with chicken atherosclerosis. I am glad that Dr. Follis is interested in both pathology and nutrition. Next, I am going to call upon Dr. Richard Follis.

DR. FOLLIS: My primary interest has been in deficiency disease, and I should like to point out a few of the gaps in our knowledge of such disease in human beings.

Today, we have considerable information on the effects of deficiencies of specific nutrients (such as the elements, vitamins, and aminoacids) on animals (rats, mice and guinea pigs). We also have some information on what happens in human beings and in primates when such deficiencies are induced.

I might digress for a moment to state that classical nutritional disease, as it occurs endemically, is not seen in this country today. We seldom see pellagra, rickets or scurvy; but these diseases are seen elsewhere. Some of the great gaps in our knowledge at the moment are: What is the pathogenesis of beriberi? What is the pathogenesis of pellagra? What are the various multiple deficiencies that may lead to the development of these diseases?

It has already been brought out that effects observed in rats, guinea pigs, or even monkeys, cannot be transposed to human beings. Recently, we have been studying the use of certain natural foodstuffs, such as corn and rice. The syndrome that develops in rats fed a diet of corn is quite different from the syndrome that develops in monkeys fed an identical diet of corn.

We have to study human diseases as they occur endemically, and this has not been done by modern methods. We have some information, but not enough. At present, our knowledge concerning certain nutritional diseases as seen in human beings is extremely tenuous. A critical appraisal of the literature on beriberi, pellagra or endemic goiter reveals that we do not know what takes place from the very beginning of the disease to the time when it manifests itself chemically or clinically. This is an extremely important subject, though not as important in this country as in some others, because diets are supposed to be fairly adequate here.

A specific problem which confronts the pathologist, and one to which the 2 previous speakers made reference, is the matter of gaps in our knowledge in the interpretation of arteriosclerosis. Among pathologists, there is no uniformity of approach to an appraisal of arteriosclerosis at necropsy. Within the last few months, this had led the World Health Organization and the Public Health Service of this country to call a conference which will be attended by pathologists from various parts of the world. They will attempt to develop a common language with regard to arteriosclerosis, so that the person who looks at an aorta in Guatemala City for instance, will make the same appraisal as to severity as the one who looks at an aorta in Boston, or some other city. Grade 2 in one area can be Grade 4 elsewhere, because the pathologists have no clear concept of the degrees of severity in certain areas. Consequently, we do not have the criteria that would permit a group of persons to sit around a table, exchange aortas, and come to agreement.

We must fill in the tremendous gaps in our knowledge, if we are to be able to say precisely that, in such and such a place, when such and such a diet is used, hypo- or hypercholesterolemia has a specific effect on the prevalence of arteriosclerosis.

MODERATOR MCCAY: Thank you, Dr. Follis.

As an animal nutritionist, I am always pleased to hear people like Dr. Follis stress the need for far more work upon human beings. We are neglecting our vast reservoirs of human material which could just as well be used for study of

the diets that we are using. I first became aware of this when I watched Guy Clark's study of calcium balance in San Quentin. He had almost an all-murderer group of life-time prisoners. They watched their diets and seemed to enjoy the regimen. Later, when working in mental hospitals on diets for spastic feebleminded subjects, I came to realize what a large group of people were available there for testing whether or not certain foods are good for children.

Many things we do not know; yet we are constantly neglecting our opportunities to use human material. As far as we know, we would do no harm but gain valuable results. In many instances, we shall have no answers until we undertake such studies.

Dr. William Kountz of St. Louis is next on our program. Dr. Kountz.

DR. KOUNTZ: I am not a nutritionist but am interested in clinical medicine. We have a research laboratory which we are preparing for use in the study of some of the dietary faults and difficulties of older people.

I am not going to discuss nutrition in the sense of feeding. Proper nutrition in the older age group does not mean that attention should be paid primarily to food intake. It means that we are dealing with persons who differ metabolically from children or young adults, and even from one another. Therefore, any program that may be good for one may not be good for another person of the same age.

In younger life some people tend to be heavy, whereas some need to gain weight. Older people differ as much or more than younger ones, with respect to activity and function of the body.

In the first place, older persons have defects in the sugar-burning mechanism (revealed by glucose tolerance curves) as compared with younger persons. The percentage of normal sugar tolerance curves among 10,000 sugar tolerance tests is relatively small. The defects vary from a delayed rise or a delayed return, to mild-diabetic and diabetic-type responses. In younger persons the curves usually are flat, hypoglycemic, or normal. Thus when older persons are fed carbohydrates and certain sugars, the metabolism tends towards the diabetic pattern.

One of the principles learned from such a study is that in oldsters there is an internal defect of utilization of food substances. Not only is carbohydrate metabolism affected, but protein metabolism also. Apparently the digestive process for protein is deficient in older people. The protein molecule may be broken down to polypeptides, but is not reduced to the amino-acid stage. Therefore, there is a deficiency of amino-acid.

Perhaps the failure to break up the protein molecule is due to a defect of the gastro-intestinal tract. This brings up the point that, in the study of individual nutrition, the gastro-intestinal tract should be evaluated. If hydrochloric acid, enzymes or bile salts are needed, they should be supplied as supplements.

The body tends to lose protein. Most older persons, and some younger ones under stress, are easily thrown into a state of negative nitrogen balance, resulting in loss of body protein from muscle, bone and other tissues. The loss cannot be reversed without difficulty. This undoubtedly leads to the development of many of the processes that we recognize as degenerative changes. It has been our experience that in many forms of disease in older people, the body is in a state of

negative nitrogen balance. Not only the feeding of extra protein, but the proper application and administration of the products of the glands of internal secretion (especially androgen, estrogen, thyroid and insulin) are important aids in preventing loss of protein. This, in turn, may prevent loss of calcium and other minerals.

In a study of the zone electrophoresis pattern of the plasma in older persons, we have found that alpha-1 lipoprotein is decreased and beta lipoprotein is increased, and that this is a fairly typical manifestation of the process of aging. What this means is not clear, but it is believed to be associated with disturbed utilization of fat—which may be corrected by diet and hormones.

It is important to recognize the low levels of vitamins, particularly of A, C (ascorbic acid) and B (thiamine, niacin and riboflavin), in older people. The deficiencies should be made up with an adequate diet, or by supplementation of the diet with these vitamins. Their biologic value is difficult to analyze. Minerals, particularly iron and calcium, should be supplied adequately when there is need for them.

To summarize, the average older person is not what he used to be because of certain deficiencies of body activity. He cannot be fed back to normal. He must be helped, particularly with hormones, with digestive aids, and with certain vitamins and minerals.

MODERATOR MCCAY: Dr. Kountz. It used to be said with regard to the Navy that the submarine service was not what it used to be, and somebody said: "It never was."

With regard to Dr. Kountz being a nutritionist, I must confess that I knew him as a nutritionist long before I knew he was an eminent clinician in St. Louis. I thought he was a biochemist in nutrition research. He forgets that some of us know different facets of his life.

Several good questions have been handed to us. One deals with sitosterol. To review its chemistry—if I remember rightly, it has the same structure as cholesterol but contains another methyl group. It is a plant product derived from soybean oil. Some time ago, sitosterol was marketed by Eli Lilly and Company. Perhaps some of you have used it. Apparently it was marketed because some experimental work indicated that it could bind cholesterol in such a manner that the cholesterol could be carried from the intestines. The hypothesis was that it would bind not only food cholesterol, because of its related structure, but also would bind part of the cholesterol synthesized by the body and poured into the intestine with the bile.

The first question is: *What are the advantages or disadvantages of sitosterol in place of fat restriction for lowering the level of blood cholesterol?* Dr. Waife, can you answer that?

DR. WAIFE: Yes, I think you answered the question in part, Dr. McCay, in speaking of the physiologic action of this substance. The information that I have indicates that sitosterol is completely nontoxic. As far as I know, there are no reports of any side-reactions. It apparently has no action other than binding, or forming a complex with, both exogenous and endogenous cholesterol. It is

taken in relatively large amounts—a tablespoonful with food, at meals—so that it is present in the intestine at the same time as exogenous cholesterol from food.

In 75 to 80 per cent of patients with hypercholesterolemia—the condition for which sitosterol is indicated—it produces a fall in the concentration of blood cholesterol, first noted after a week or two. By three or four weeks, a fairly normal level is reached and maintained as long as sitosterol is administered.

The amount of fall apparently depends upon the initial level. That is, if the cholesterol level were initially 400 mg. per 100 ml., it might be decreased to about 300 or 285 mg. per 100 ml. However, if the initial level were only 285 mg. per 100 ml., the amount of fall would not be as great. The fall is approximately 25 to 30 per cent.

Sitosterol is apparently quite palatable. Most patients seem to take it without difficulty. Certain patients do not respond. As far as I know, there is no information as to why this occurs or whether the metabolism is different in these cases; nor is there any criterion for predicting who will or will not respond.

If one believes that a high level of blood cholesterol is a significant factor in the pathogenesis of atherosclerosis, then, logically, one should try to lower the cholesterol level. Lower levels can be obtained by use of a sitosterol preparation than with a reduction in the intake of fat, because a person cannot be maintained on a fat-free diet. It is totally unpalatable and impracticable. Sitosterol offers a reasonable approach to the problem. It is not the whole answer, but it is probably the most practical means at present for lowering the serum cholesterol level.

MODERATOR MCCAY: Thank you, Dr. Waife.

Here is a question for you, Dr. Kountz: *Do all older people have an increase in lipoproteins?*

DR. KOUNTZ: In our experience, yes. There is a change in lipoproteins which can be modified. Diet plays a part.

When the diet is not high in fat, there is relatively less change in lipoproteins when the patients receive hormones—androgens, particularly. When dietary fat is reduced, there is usually no change.

MODERATOR MCCAY: Dr. Kountz, another question is: *Have you been able to alter the lipoproteins in the serum of old people?* Do you want to say more about that?

DR. KOUNTZ: That has been our experience. Hormonal substances and diet will modify it.

MODERATOR MCCAY: Here is one for Dr. Follis: *Does the preservation of food products through freezing and canning reduce their vitamin and nutritional value?* I am not certain that you discussed that in your book, Dr. Follis.

DR. FOLLIS: That is more in your line, isn't it?

MODERATOR MCCAY: Perhaps so. Preservation does, to a limited extent affect vitamin values; freezing, only slightly. Preservation by canning reduces the B vitamin content substantially, perhaps by one third, and preservation by radiation reduces it to about the same extent.

MODERATOR MCCAY: *Please discuss the importance of carbohydrate in relation to the nutrition of the heart muscle.* Dr. Follis.

DR. FOLLIS: This is a fundamental biochemical question which I cannot discuss thoroughly in a short time.

The nutrients for the heart muscle are primarily carbohydrates—pyruvate and glucose—although fatty acids are also involved. I do not know what the person asking the question has in mind. Of course, the heart is dependent upon any number of nutrients—metallic elements, as well as carbohydrate and vitamins. This is too broad a subject.

MODERATOR MCCAY: We have many questions here. I want to start with some of those on cholesterol.

Should we stop feeding infants and children a high-fat diet? Dr. Jolliffe.

DR. JOLLFFE: That certainly is a common question. We do not have the data with which to furnish the answer.

There is little evidence at present to indicate that the ordinary high-fat diet of infants does much damage. We answer it this way: It is undesirable, because you expect infants and children to grow to be adults. Therefore, it is best not to cultivate the habit of a high-fat diet.

Studies are in progress with infant diets made according to basic formulae. The fat content of the diet is altered but the protein and other ingredients remain the same. In other words, when butter fat, corn oil, or mother's milk fat is added to a skimmed-milk formula diet, the level of blood cholesterol can be influenced rapidly.

In the nursing infant, initial blood cholesterol concentrations of 100 to 110 mg. per 100 ml. can be raised to high levels by administering certain of the fats that are commonly used in feeding infants, as compared to the fat of mother's milk.

How important this observation is, I do not know.

MODERATOR MCCAY: Dr. Follis?

DR. FOLLIS: Might it not be true, though, Dr. Jolliffe, that deposits of lipid that may be seen after the age of 10 and at the time of puberty can be modified by diets low in fat, if low-fat diets were started initially?

DR. JOLLIFFE: My thought is that we shall possibly reach that stage, or change the quality of the fat given to infants.

When my son was born, it was the practice to remove infants from the mother's breast and give them an evaporated milk formula diet. It may be that this is a factor in the high rate of coronary occlusion among people 30 to 40 years old today.

MODERATOR MCCAY: *What is the relation between alcohol and atherosclerosis?* Dr. Kountz, I think you had some ideas about that.

DR. KOUNTZ: How to advise people with arteriosclerosis about the use of alcohol is a common problem in clinical medicine. Abstinence from alcohol is not a cure-all. As a matter of fact, when alcohol is injected into patients with peripheral arterial disease, about the only improvement observed is that which occurs during the period of alcoholic debauch. It is like any other nutritional problem. Too much sugar in the diet of the older person is not desirable because it places a strain on the carbohydrate-burning mechanism; usually the result is

the development of fat. That brings up another question: What happens to body fat under the circumstances of a starvation diet? Does the cholesterol level rise when the body fat is burned?

Alcohol, in moderation, is well tolerated by most older people. It acts as food; it is burned as a carbohydrate. However, we would not recommend it highly.

DR. JOLLIFFE: I am told that it is neither hypo- nor hypercholesterolemic.

DR. KOUNTZ: It has a slight cholesterologenic effect.

MODERATOR MCCAY: Here are 2 questions that may or may not be related.

Some of my friends who are clinicians are using large amounts of niacinamide for arthritis. The first of these questions is: *What diets are used in rheumatoid arthritis and osteoarthritis?* The second concerns cholesterol: *How does the use of nicotinic acid in high dosage compare with other methods for reducing the blood cholesterol level?* Dr. Waife, have you this information?

DR. WAIFE: I know of 2 reports, one from the Mayo Clinic and the other from Dr. Altschul in Canada, to the effect that nicotinic acid (not the amide) reduces the blood cholesterol level rather rapidly. Neither report, as I remember, offered any explanation. It may be purely a "physiologic artifact."

MODERATOR MCCAY: Perhaps we can put some of the questions together:

1) *Much has been written about fat in the diet with relation to nutrition and aging. Can the panel suggest any specific answers at this time for the general practitioner or internist? Are total calories more important or less important than the types or amounts of fat?*

2) *In a recent press release, an investigator warned against steaks as a potential source of atherosclerosis. This important pronouncement has provoked many lay inquiries. Will one of the panelists please comment?*

3) *What types of fat would you include in the diet?*

4) *Dr. Kaufman has stated that a reduction of fats lowers the level of blood cholesterol, but does not decrease the S_f factors. What are your findings?*

5) *Is there any known complication or danger in severe restriction of fat in one's diet?*

Would you like to try those, Dr. Jolliffe?

DR. JOLLIFFE: With regard to the last question—There are no known complications or dangers of reducing the fat in the diet to the level recommended. Most investigators advise lowering dietary fat to between 25 and 30 per cent of the total calories. That is neither severe nor drastic, nor is it any of the other names that people sometimes apply to such a recommendation. It is not elimination of fat; it is only a moderate reduction. Even at that, the level is considerably above the amount in the diet of Italians, Portuguese, Spaniards and many other Mediterranean peoples, and twice that in the diet of the Japanese and people of many other countries.

There are no known complications to removing the visible fat from meat, eliminating butter and margarine, and omitting fried foods from the diet. There would still be 20 to 25 per cent fat in the diet.

Question 3, about what types of fat should be included in the diet. My recommendation is to reduce the total fat below 30 per cent, that is, to 25 to 30 per

cent of the total calories, and to include in that a reasonable amount of salad oils—say, an ounce of corn, cottonseed or soybean oil. Fish should be included in the diet. The fattest of fish contains less fat than the leanest steak, roast beef or mutton chop. Besides, the fat in fish is of the unsaturated type.

Question 2, regarding the warning against steaks as a potential source of atherosclerosis. My guess is that that was a misinterpretation. I have not heard this investigator warn against eating steak, but I have heard him recommend caution about eating the big rim of fat around a steak, saying to leave that on the plate. We do not need that rim of fat anyhow, for calories or for any other reason. I would be surprised if meat, in itself, proved to be atherogenic. *Homo sapiens* has been eating meat ever since he has been *homo sapiens*, and I cannot believe that a reasonable amount of the fat distributed through the lean part of the meat will cause atherosclerosis. Otherwise, we would not be here today.

MODERATOR MCCAY: Much of this is contained in your textbook, is it not?

DR. JOLLIFFE: Yes. It is all written there.

MODERATOR MCCAY: Most of us have his textbook, I take it, judging from the number sold.

Some of these questions are difficult to answer, but they are questions that we receive from the public all the time. One of them is: *What is the present status of glutamic acid derivatives in cerebral metabolism? Are they valid in therapy?* Dr. Kountz, is that yours?

DR. KOUNTZ: I could not answer it.

MODERATOR MCCAY: They are thinking back to the work of Himwich, are they not?

DR. KOUNTZ: Yes.

MODERATOR MCCAY: Dr. Follis, would you like to try that?

DR. FOLLIS: Obviously, glutamic acid is of importance in the metabolism of the brain. It is my understanding that these materials have not been effective therapeutically. I think Dr. Waife would know more about that than I.

MODERATOR MCCAY: Yes, Dr. Himwich has written an article or two on that.

DR. WAIFE: I agree with what Dr. Follis said. I have had no direct experience, but the general conclusion seems to be that, although there is some evidence that glutamic acid is metabolized by the brain (as are many other compounds), it is not of much value therapeutically.

MODERATOR MCCAY: You think that therapeutically it is not worth while? It has had tremendous publicity, has it not? The public is very much aware of it.

Is the cholesterol level affected by nervous tension? Dr. Kountz, is that your question?

DR. KOUNTZ: I think not directly. Tension affects metabolism in general. It affects the burning of carbohydrates. It may also affect nitrogen balance, but only temporarily. I do not think that tension would be considered as a factor on a long-term basis.

MODERATOR MCCAY: With regard to tension, the experiments of the manufacturers of tranquilizer drugs have been interesting. All of them seem to be feeding chickens. I think the next thing we shall see in chicken feeds is a tran-

quilizer. The producers are hoping to keep tension down during feeding and thus fatten the chickens a little more cheaply.

This is a difficult one: *Is there any relationship among epinephrine, norepinephrine ratio, fat metabolism, and cholesterol?* Would anyone have an answer to that? This is a specific and technical question. Dr. Kountz, you gave a paper on drugs the other day. I wonder if you would discuss that?

DR. KOUNTZ: I think it best to skip that.

MODERATOR MCCAY: Either Dr. Follis or Dr. Waife? We are at a standstill. Perhaps we can take up the rest of the cholesterol question, if you are willing, Dr. Jolliffe.

DR. JOLLIFFE: The remainder of the questions on cholesteral have to do with safe levels, what is normal, and so forth. I can't answer that, but I can tell you this: In the cooperative study reported last October in *Circulation* involving about 5,000 cholesterol determinations in men from 40 to 65 years of age, the 50 percentile point was a level of about 240 mg. per 100 ml. That means that the cholesterol levels of half of the men in that age range were above, and the other half below. This was in the United States. Taking the percentile points from all over the world—including the Japanese, the Bantus and the Italians—the 50 percentile level would come nearer to 180 or 200 mg. per 100 ml.

My thought is that a normal concentration of blood cholesterol for that age group should be below 220 mg. per 100 ml., preferably below 200 mg.; 160 mg. would not be abnormally low, if it could be brought to that level by a diet otherwise adequate.

Is the quantitative estimation of serum cholesterol well enough standardized in ordinary hospital laboratories to be of value to the clinician? I do not know whether it is or not in actuality, but it could be.

Is there any difference between animal and vegetable fat in relationship to the cholesterol level? There is an argument now as to whether the difference in fats is due to the degree of total unsaturation as measured by the iodine number, or due only to the polyunsaturated essential fatty acids. In general, liquid fats do not affect, or else they lower, the blood cholesterol level. Solid fats, whether they are of animal or vegetable origin, generally increase the blood cholesterol level. Solid fats are ordinarily cooking fats and margarines that have been hydrogenated (as all of them have), and mutton, beef and pork fat. Chicken fat and fish fat are much less saturated. Some vegetable fats, like coconut oil and cocoa fat, are highly saturated and tend to increase the blood cholesterol concentration.

What is the relation of cellular metabolism to the blood cholesterol level? I do not know that I can answer that question. What does it mean?

Could thyroid therapy be used in lowering the blood cholesterol level? In hypothyroid subjects, yes. In euthyroid subjects—I cannot answer.

MODERATOR MCCAY: Here is another question on thyroid function, Dr. Kountz. *What is the relation of thyroid function to cholesterol levels, particularly with regard to evaluation of hypercholesterolemia?*

DR. KOUNTZ: It has been known for many years that hypothyroidism is associated with an increased concentration of cholesterol in the blood. How this happens, no one knows, except that it probably represents failure to burn fat.

There may be something of value in the finding by Lou Katz and others that, in order to produce atherosclerosis in a dog, one must either feed him thiouracil or remove the thyroid gland. It has also been shown that in animals like chickens atherosclerosis does not develop when thyroid is fed. Thus, there is an important relationship between deficient thyroid function and atherosclerosis.

It is necessary to emphasize that the entire group of endocrine glands must play an important role in this metabolism. Perhaps some day we shall not pay as much attention to the diet as to the state of body health.

DR. JOLLIFFE: May I comment?

An interesting observation is that the number of people with hyperthyroidism who have had a myocardial infarction can be counted on the fingers of one hand. If tension were going to produce myocardial infarction, one would expect more cases of myocardial infarction in that group.

MODERATOR MCCAY: I have 2 more questions. The first of these is long and difficult: *Will you enumerate some objectionable changes, subtle ones, in nutritive values of processed foods, in a broad sense, with regard to their known and conjectured effects upon health, particularly in the aged?* We can say briefly that people often fail to realize that the millions spent in industrial research are spent largely for the sophistication of foods—to make them look better, to make them taste better, to make the housewife buy them. Attention is seldom paid to nutritive values. That is the reason we have had so much trouble when we have tried to introduce better bread or anything else. The effort is always directed toward sophistication and easier manufacture. This trend has been seen throughout the food industry.

Dr. Kountz has already stressed the excessive use of sugar, and Dr. Jolliffe has stressed the excessive use of hydrogenated fats. Hydrogenated fats are convenient to use. They do not smoke when raised to a high temperature. Even peanut butter has been hydrogenated. It is hard to find nonhydrogenated peanut butter on the market. Because it has a slightly greater plastic quality, the housewife is expected to buy the hydrogenated product more readily.

We have tended always to modify foods in order to obtain a quality that will sell the product, and to pay little attention to the destruction of nutritive value.

Few people realize the admirable job that Representative Delaney, from Queens, is trying to do with regard to the Food and Drug Administration. He is trying to have a law passed to prohibit putting into food any chemical known to be injurious (thus, no carcinogenic agent could be used) or that does not enhance the nutritive value of the food. Of course, the industry is fighting him tooth and nail, because they like to put chemicals into bread so that the housewife cannot tell stale bread from fresh bread. Food processors do many things like that. Unless Delaney gains more support, the bill for which he is so admirably fighting will certainly be defeated.

The final question is, *What is the Department of Health, Education, and Welfare doing to encourage the study of the relation between disease and nutrition?* We can answer this in part. They have a vast program, and it has been growing steadily. Last week, I saw a picture of those fat rats that one of the workers in Bethesda is producing—the fattest rats I have ever seen. There is a great deal of work going on at the National Institutes of Health. In terms of grants and millions

of dollars per year, it must be a very expensive program. Perhaps someone in the panel knows about the allotting of grants for these projects. Does anyone have an idea?

DR. FOLLIS: I can say from personal experience, because I am on one of the study sections of the National Institutes of Health, that a good deal of money is going into nutrition. The Institute for Arthritis and Metabolism is particularly interested in nutrition.

Within my own experience, the National Institutes of Health have recently given a grant to a committee interested in studying the pathology of nutritional disease, in order to enable us to hold a conference dealing with present-day concepts and understanding of certain human nutritional disorders such as beriberi and hypovitaminosis A. The national government, so far as the Department of Health, Education, and Welfare is concerned, is thus vitally interested in nutritional problems.

Other groups like the Department of Agriculture are interested in this subject as well. A committee called the Interdepartmental Committee for Nutrition for National Defense, composed of the Department of Health, Education, and Welfare, the Department of Defense, the Department of Agriculture, and the State Department is particularly interested in the nutrition of our allies. Surveys have been made in Pakistan, Iran, Turkey, Formosa, and other areas in which we are vitally involved from the standpoint of defense.

MODERATOR MCCAY: Are there any more comments from the panel? If not, we thank the audience for the many questions that we are going to save and mull over later.

FUNCTION OF THE POSTMENOPAUSAL OVARY. COMPARISON OF URINARY ESTROGEN AND GONADOTROPIN EXCRETION AND RESPONSE TO ADMINISTRATION OF FSH IN POSTMENOPAUSAL AND OVARIECTOMIZED WOMEN*†

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After the menopause, reproductive capacity is lost, but there is evidence that estrogen production is continued. For example, estrogens can be extracted from the urine of postmenopausal women, evidence of estrogenic activity not infrequently can be seen in endometrial biopsy specimens, and vaginal smear examinations may show changes suggestive of estrogen effect. The origin of this estrogen, however, is not entirely clear. Heller, Farney and Myers (1), observing the abrupt increase of climacteric symptoms after the removal of postmenopausal ovaries, suggested that the ovary was the most important site of postmenopausal estrogen production. Hertig (2), studying the histologic structure of aging ovaries, concluded that the stromal cells may assume secretory function.

There is considerable evidence that the adrenal cortex is a source of estrogen production. Dao (3) recovered estrogens from the urine of ovariectomized patients having carcinoma of the breast. Hershel Sandberg and co-workers (4) induced increased excretion of estrogen in ovariectomized but otherwise normal women, by the administration of ACTH. West, Damast and Pearson (5) observed similar increases in estrogen excretion in patients with mammary carcinoma who received ACTH.

It is the purpose of this report to present studies in which postmenopausal ovarian function was evaluated in the following manner:

1. The urinary estrogen and gonadotropin excretion of 51 normal postmenopausal women was assayed and compared to that of 30 surgically castrated patients.

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2. Pituitary follicle-stimulating hormone (FSH) was administered to 6 postmenopausal women and 2 castrated women. Urinary estrogen excretion was used as the criterion of response.

PATIENTS

Fifty-one postmenopausal women were studied. Their ages ranged from 45 to 81 years, and the menses had ceased from one to thirty-three years before study. The only one of these women who had undergone pelvic surgery was 65 years old, and had had a uterine suspension at the age of 45 years. Thirty-three were normal postmenopausal women seen consecutively at a cancer detection clinic, and 18 were seen because of menopausal symptoms at the Endocrine Clinic of Detroit Receiving Hospital.

Thirty castrated patients whose ages ranged from 23 to 52 years were studied from one month to thirteen years following bilateral ovariectomy. Neither the postmenopausal nor the castrated patients had received endocrine therapy for at least three months prior to study and all were in apparent good health.

Urinary estrogens were determined in each of the 51 postmenopausal women and in 24 of the 30 castrated patients. Urinary gonadotropins were determined in 47 of the postmenopausal women and in 18 of the castrated women. Normal values for women of reproductive age were established by assaying the urinary estrogen and gonadotropin excretion of 27 regularly menstruating women, 19 to 36 years of age.

METHODS

Urinary estrogens were assayed biologically by a method described elsewhere in detail (6). In this method, acid hydrolysis is used, and the sodium hydroxide-soluble fraction of the chloroform extract is administered to immature female rats. Increases in uterine weight produced by 2 or more dilutions of the urine extract are compared with responses produced by estradiol benzoate, and the results are expressed as micrograms of this estrogen per 24-hour urine specimen.[1]

Urinary gonadotropins were concentrated from urine by ultrafiltration and assayed in immature female rats. In assaying the gonadotropins of postmenopausal and castrated women, the concentrate equivalent to a 3-hour aliquot of urine (*i.e.*, one-eighth of the concentrate from a 24-hour specimen) was administered to each of 4 immature rats. In assaying the urinary gonadotropins of women of reproductive age, the concentrate from a 12-hour aliquot of urine was administered to each of 4 rats. Results are expressed as the average ovarian weight for the 4 assay rats.

FSH (follicle-stimulating hormone) prepared from hog pituitary glands[2] was administered intramuscularly in a dosage of 25 units twice daily for two to three weeks.

RESULTS

Urinary excretion

Urinary estrogen excretion for the 51 postmenopausal women averaged 0.35 microgram per twenty-four hours—approximately twice that of the 24 castrated women, whose average excretion was 0.17 microgram (Fig. 1). Statistical analysis showed this difference to be highly significant, the probability that the difference was due to chance being less than 0.01 ($t = 2.97$) (Table 1). The average estrogen

[1] The lower limits of sensitivity, using this assay method, are 0.2 microgram per twenty-four hours. Specimens that contained less than this amount were arbitrarily assigned the value of 0.1 microgram per twenty-four hours for purposes of statistical analysis.

[2] Generously supplied by Armour Laboratories, Chicago, Illinois.

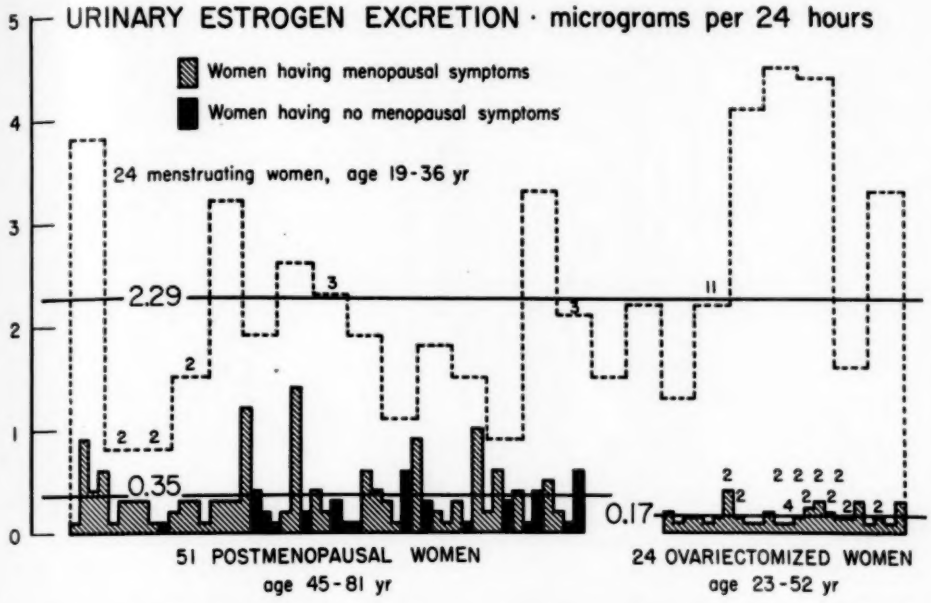

FIG. 1. Data on the normally menstruating, postmenopausal and ovariectomized patients are arranged along the abscissa from left to right according to increasing age, years after the menopause, and time since castration, respectively. When more than 1 observation was made per patient, the bar indicates the average and the digits above the bar represent the total number of observations.

TABLE 1

Urinary Estrogen Excretion of Postmenopausal, Castrated and Regularly Menstruating Women

Subjects	Range of Age (yrs.)	No. of Subjects	Urinary Estrogen (μg./24 hrs.) (mean ± S.E.)
Postmenopausal	45–81	51	0.35 ± 0.04
Castrated	23–52	24	0.17 ± 0.02
Regularly menstruating	19–36	24	2.29 ± 0.23

excretion of the regularly menstruating women was 2.29 micrograms per twenty-four hours. The individual values, arranged according to the time of the menstrual cycle, are shown in Figure 2.

In Figure 3, the individual values for the postmenopausal women are grouped according to the number of years after the menopause. Estrogen excretion remained constant throughout the postmenopausal years; the average value for women sixteen to thirty-three years after the menopause was the same as that for women one to five years after the menopause. The length of time after castration had no apparent effect on urinary estrogen excretion; the average value for 10 patients studied one to six months after ovariectomy was the same as that for 14 patients studied one to fourteen years after operation.

No correlation was observed between urinary estrogen levels and the presence

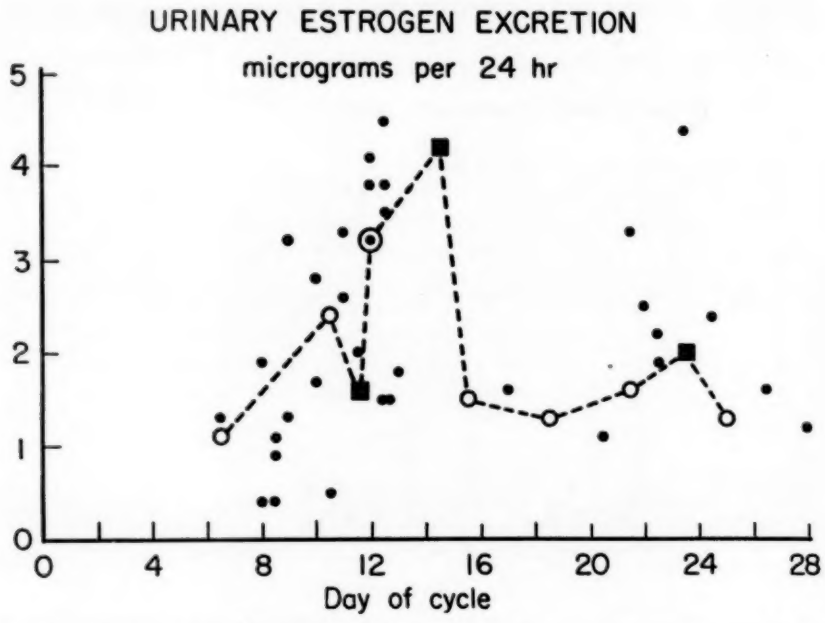

FIG. 2. Scattergram representing individual urinary estrogen excretions of 24 normal menstruating women arranged according to the day of the cycle. The dotted line connects the estrogen excretion values of Subject S. S., aged 26 years, who collected 11 specimens during 3 menstrual cycles depicted as ○, ⊙ and ■.

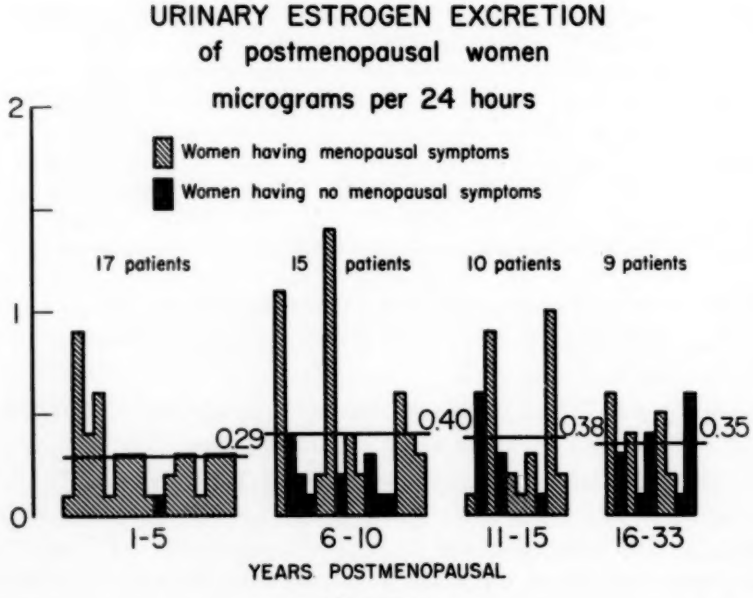

FIGURE 3

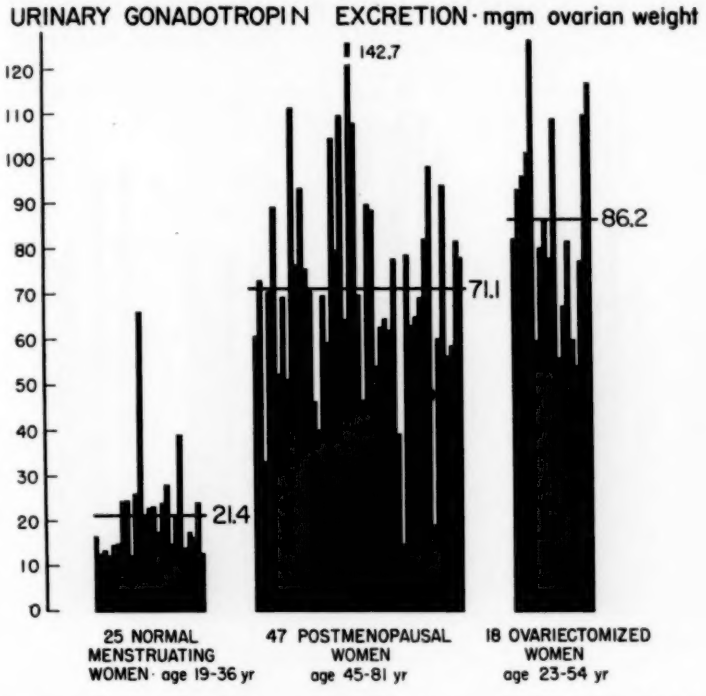

FIG. 4. The three groups of patients are arranged according to increasing age, years after the menopause, and time since castration, as in Figure 1. In assaying the urine of normal menstruating women, four times as much urine concentrate was administered per assay rat (12-hour aliquots) as in assaying the urine of postmenopausal and ovariectomized women (3-hour aliquots).

TABLE 2

Urinary Gonadotropin Excretion of Postmenopausal, Castrated and Regularly Menstruating Women

Subjects	Range of Age (yrs.)	No. of Subjects	Mean Rat Ovarian Wt. (mg.)	S.E.
Postmenopausal women.....	45–81	47	71.1	±2.10
Castrated women.....	23–54	18	86.2	±3.25
Menstruating women.....	19–36	25	21.4	±2.20
			In 53 control rats (no injection) 11.0*	

* This figure represents the accumulated control data for all of the gonadotropin and estrogen assays performed in this study.

or absence of menopausal symptoms. The average estrogen excretion of the 35 postmenopausal women who had symptoms at the time of study was not significantly different than that of the 16 women who lacked symptoms (Fig. 3). Each of the ovariectomized patients had typical menopausal symptoms, including hot flashes. The symptoms, in general, were more severe than those experienced by the postmenopausal women.

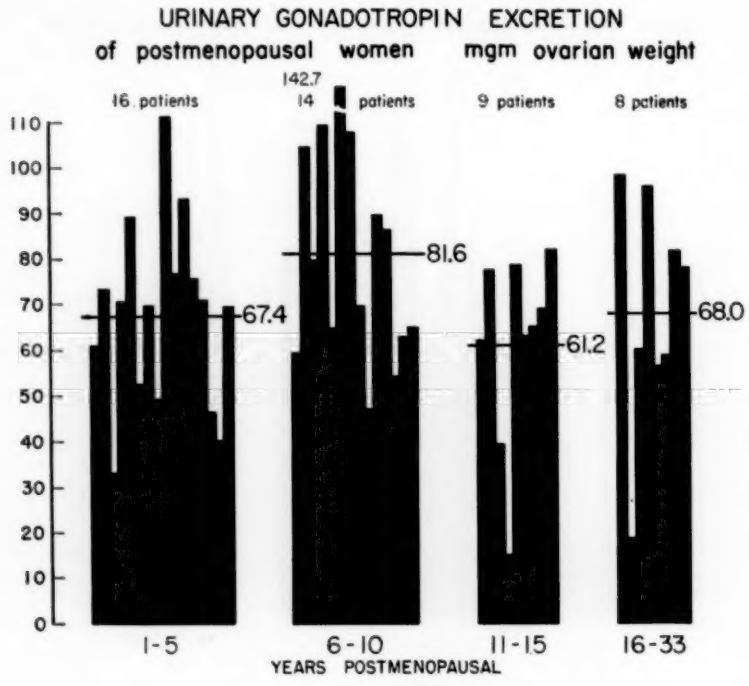

FIGURE 5

Urinary gonadotropin excretion was elevated in each of the postmenopausal and castrated women (Fig. 4). Values for the individual patients were at least 4 to 8 times as great as those found in normal menstruating women. The average of the values for postmenopausal women (71.1 mg.) was not as high as that for the castrated women (86.2 mg.). This difference is highly significant, the probability that it was due to chance being less than 0.001 ($t = 3.7$) (Table 2).

Urinary gonadotropin excretion remained elevated throughout the postmenopausal years. There was no significant difference between groups when the values were arranged according to years after cessation of menses (Fig. 5).

Individual values for gonadotropin excretion (arranged according to the time of the menstrual cycle) for 25 normal menstruating women are listed in Table 3.

Response to administration of FSH (Table 4)

Two of 6 postmenopausal women (N. R. and V. S.) showed definite evidence of ovarian stimulation while receiving hog pituitary FSH (Figs. 6 and 7). Urinary estrogen excretion increased to levels found in regularly menstruating women and then returned to pretreatment levels upon discontinuing FSH. Concomitant with the decrease in urinary estrogen excretion, Subject V. S. experienced a three-day period of vaginal bleeding. Both V. S. and N. R. were having moderately severe menopausal symptoms, which were ameliorated while they were receiving FSH. Estrogen excretion did not change and symptomatology was not altered

TABLE 3

Urinary Gonadotropin Excretion of 25 Regularly Menstruating Women

Subject	Age (yrs.)	Days of Menstrual Cycle: 1–11			12–15			16–30		
		No. of Assay Rats*	Uterine Wt.**	Ovarian Wt. (mg.)	No. of Assay Rats*	Uterine Wt.**	Ovarian Wt. (mg.)	No. of Assay Rats*	Uterine Wt.**	Ovarian Wt. (mg.)
A. J.	19				2	+, +	16.5			
E. S.	20	4	+, +, −, −	13.5				4	−, −, −, −	12.0
R. A.	20	4	−, −, −, −	12.0				4	−, −, −, −	13.0
		2	+, −	18.0						
N. D.	21	2	−, −	12.0	4	+, +, +, +	12.0	2	−, −	13.0
L. U.	21	4	+, +, +, +	18.5				4	−, −, −, −	11.0
V. K.	21	2	+, +	24.0	2	−, −	6.0			
M. J.	21							4	+, +, +, +	24.2
J. W.	22	4	+, +, +, +	24.2						
L. S.	22	2	−, −	13.0				2	−, −	11.5
		2	−, −	12.0						
P. S.	23	4	+, +, +, +	35.0				3	−, −, −	14.0
P. Y.	23							2	+, +	66.0
I. D.	23				2	−, −	17.0	2	+, +	24.5
H. E.	23				3	+, +, +	23.0			
P. S.	24				4	+, +, +, +	23.5			
Z. K.	24	4	+, +, +, +	22.2				4	+, +, +, +	13.5
B. G.	24				2	+, +	29.0			
M. C.	24				2	+, +	24.0			
B. R.	25	3	−, −, −	17.0				3	+, +, +	11.3
		4	+, +, +, +	16.0						
G. O.	25				3	−, −, −	21.3			
J. O.	26	3	+, +, +	39.0						
S. S.	26	2	+, +	18.0				2	−, −	10.0
H. L.	27				2	−, −	12.5			
					2	+, +	23.0			
E. L.	28				3	+, +, +	16.3			
L. T.	29							4	+, +, +, +	24.0
B. B.	36				2	−, −	13.0			

* Given 12-hour aliquot of urine concentrate per assay rat.

** The plus sign designates a uterine weight of 60 mg. or more.

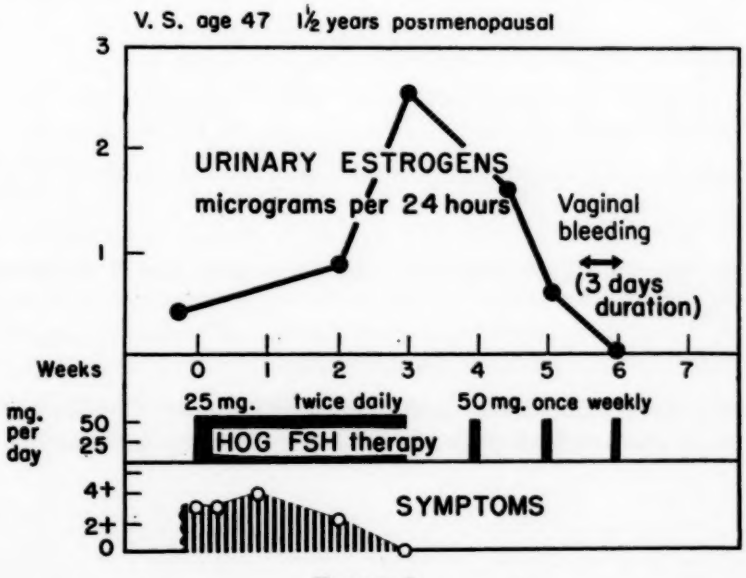

FIGURE 6

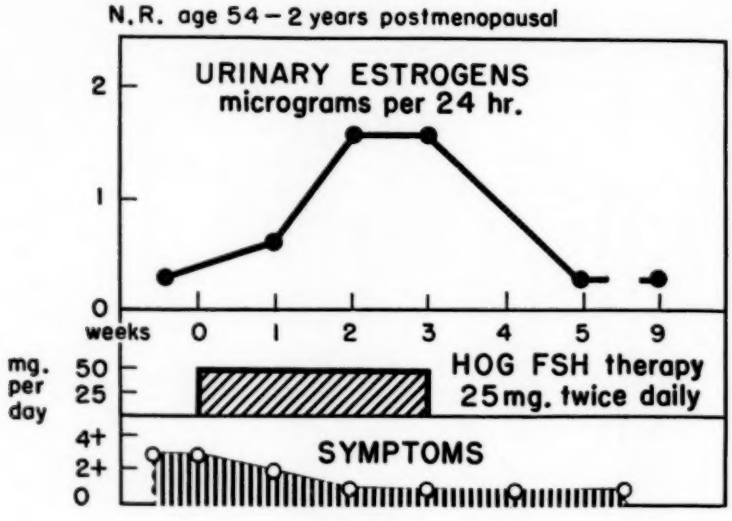

FIGURE 7

TABLE 4

Urinary Estrogen Excretion in Postmenopausal and Castrated Women Receiving Hog FSH

Subject	Age (yrs.) and time after menopause or surgery*	Urinary gonadotropins (mg. rat ovarian wt.)	Urinary estrogens (μg./24 hrs.)				
			Pre-treatment	Hog FSH, 25 mg. twice daily intramusc. Week of treatment			Post-treatment
				1	2	3	
Postmenopausal							
H. B.	54 [12]	62.0	<0.2	<0.2	0.2	0.3	
N. R.	54 [2]	52.3	0.3	0.6	1.6	1.6	0.3
E. J.	47 [1]	60.3	<0.2	<0.2	0.3		
V. S.	47 [1½]	33.3	0.4		0.9	2.6	0.4
I. S.	54 [3]		<0.2	<0.2	<0.2	<0.2	
M. D.	56 [4]	70.5	<0.2	0.3	0.2	<0.2	
Ovariectomized							
C. B.	36 [4]	54.2	0.2	0.3	0.2		
C. T.	48 [1/12]	82.2	0.2		<0.2		

* The numbers in brackets represent the years after the menopause and after castration, respectively.

in the remaining 4 postmenopausal women and in the 2 castrated patients (Table 4).

DISCUSSION

The observation that normal postmenopausal women excrete twice as much estrogen as ovariectomized patients indicates that the postmenopausal ovary

retains some estrogen-producing function. The amount produced by all sources is relatively small, however, for in our series the postmenopausal women excreted only about one-sixth as much as women of reproductive age. This change to low estrogen production at the time of the menopause appeared to be abrupt, for after cessation of menses, estrogen excretion remained constant rather than showing a progressive decline. Pincus, Romanoff and Carlo (7) have tabulated estrogen excretion values for normal women according to decades of age. Unfortunately, they did not indicate at what age the menopause occurred. Omitting their data for the fifth and sixth decades, which undoubtedly include values for both pre- and postmenopausal women, their findings are comparable to ours. In agreement with our observations, their average values for women past 60, grouped according to decades, are constant. Furthermore, the estrogen excretion of their patients aged 60 to 99 years was approximately one-sixth that of women aged 20 to 39 years.

The ovary and the adrenal cortex are the only known sources of estrogen production in the nonpregnant woman (3, 5). Among other sources which might be considered, diet would seem the only one worthy of consideration. Estrogens have been detected in a wide variety of foodstuffs (8), but the amounts found are so small that it is highly unlikely that they would be detected in the human subject even by the sensitive biologic method for assaying estrogens. Struthers (9), observing "estrogenic effects" in the vaginal smears of castrated, adrenalectomized women, suggested that there might be sources more important than the ovary and adrenal cortex for estrogen production in postmenopausal women. It would seem more reasonable to conclude that factors other than estrogens affect vaginal cytology.

Further evidence that the postmenopausal ovary retains some degree of function was the finding that ovariectomized patients excrete significantly more gonadotropins than do postmenopausal women. Either of 2 widely held theories would explain this observation; 1) reciprocal pituitary-ovarian function, resulting in inhibition of pituitary gonadotropin secretion by estrogens, or 2) utilization of gonadotropins by functioning ovarian tissue. Regardless of which theory is applied, it is generally agreed that urinary excretion of gonadotropin is lower in subjects having functional gonadal tissue than in castrates.

The urinary gonadotropin of the postmenopausal and castrated women did not decline with advancing years. Masters (10) reported decreased excretion of gonadotropin in aged women, but his studies were performed on institutionalized patients in whom chronic debility may have been a factor.

Administration of pituitary FSH to postmenopausal women would not be expected to produce a response if plasma gonadotropin levels were elevated to the same degree as urinary gonadotropins. The somewhat unexpected observation that 2 of the 6 postmenopausal women responded to pituitary FSH suggests that their *plasma* gonadotropin levels were only slightly elevated. Since their urinary gonadotropins were markedly elevated, it would appear that only slight increases in plasma levels are necessary to produce marked increases in urinary levels.

In 2 women who responded to FSH, the menses had ceased only one year and one and a half years previously, suggesting that the ability of the ovary to respond to FSH may not be retained for any significant length of time after the menopause. Perhaps sites other than follicular structures—such as stromal cells, the function of which is not regulated by gonadotropins—are the source of estrogen production by the postmenopausal ovary.

SUMMARY AND CONCLUSIONS

Urinary estrogen and gonadotropin excretion was determined in 51 normal postmenopausal women, 45 to 81 years of age, and in 30 surgically castrated women, 23 to 52 years of age. In the postmenopausal women the menses had ceased from one to thirty-three years previously. Urinary estrogen excretion of the postmenopausal women was approximately twice that of the castrated women. Although there was overlapping, the difference between the values for the 2 groups was highly significant. Estrogen excretion remained constant throughout the postmenopausal years, being the same sixteen to thirty-three years after the menopause as one to five years thereafter.

Urinary gonadotropin excretion was elevated in each of the postmenopausal and castrated women. The average value for the ovariectomized women was significantly higher than the average for the postmenopausal women. Urinary gonadotropin excretion of the postmenopausal women showed no tendency to decrease with advancing years.

Two postmenopausal women who received hog pituitary FSH responded with increased urinary excretion of estrogen and amelioration of menopausal symptoms. The other 4 postmenopausal women and the 2 castrated patients who received pituitary FSH did not respond.

It is concluded that the postmenopausal ovary retains a small but significant secretory function and that it is the major source of postmenopausal production of estrogen.

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A NEW AID IN THE MEDICAL MANAGEMENT OF DIVERTICULITIS (300 CASES)

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Diverticulitis of the colon is a disease of adulthood, particularly in the older age groups (1). The incidence is greatest after the age of 50 years, although the disease has been known to occur in younger persons (2a). As life expectancy increases, more cases will be observed. In approximately two-thirds of patients with diverticulitis of the colon, symptoms are minimal or absent; in the remaining third, symptoms are sufficiently severe for treatment.

Despite much interest and speculation as to the etiology of diverticula of the bowel, no unanimity of opinion exists (2a). The diverticula are usually multiple and are composed of mucosa, submucosa, and serosa. As the diverticula develop, they expand into sac-like structures of varying size. They retain the small point of their origin, which acts as a collar. This is an important factor in the subsequent development of diverticulitis. Fecal matter enters the sac through the constricted neck and is confined therein by the small opening. Acquired diverticula have no muscular coat and cannot eject offending foreign material. As a result, the foreign material becomes inspissated and stagnant, soon ulcerates through the lining of the sac, and sets up an infection that may be mild or severe (2b).

Surgical attack upon diverticulitis recently has had many proponents and merits consideration in younger good-risk subjects. In fact, the younger the patient, the more logical surgical treatment becomes.

The treatment of diverticulitis, however, is primarily medical. In about 80 per cent of cases, the condition can be controlled adequately by medical means and operation can be avoided (3). Standard medical treatment has been designed to keep the pouches empty. The diet is bland, nonirritating, and free of residue. Fruits with seeds, such as berries, are to be avoided. Rough, raw, stringy vegetables, such as celery, are undesirable. Fish must be cut into filets and the bones removed. Cathartics are to be avoided, since the hyperperistalsis that they produce tends to aggravate existing inflammatory lesions. Mineral oil may be taken in liberal amounts, but not to the point of anal leakage. Colonic irrigation is contraindicated because of the danger of perforation (2c).

The medical treatment of diverticulitis becomes more effective through the use of a new type of surface-active agent, propethyleneoxides (Magnocyl)[1]. This compound is a nonionic polymer of ethylene oxide and propylene oxide (4) which reduces the surface tension of water, in which it dissolves readily. When this agent is ingested, the wetting property improves the texture of the stool so that the patient's need to strain during defecation diminishes. In my clinical experience, there has been no evidence of toxicity.

Through adherence to the accepted medical treatment with a bland, low-

[1] Magnocyl Capsules (250 mg.) were supplied by Paul B. Elder Company, Bryan, Ohio.

residue diet and the use of antibiotics, patients obtain some relief. Upon addition of propethyleneoxides to the regimen, and deletion of mineral oil, the incidence of symptoms and of complications is reduced markedly. Medical management has become definitive, so that radical surgery can be reserved for the small number of patients who fail to respond.

METHOD

The effect of propethyleneoxides was studied in 300 patients with diverticulitis over a three-year period in a 75-bed hospital with a stationary population. The family physicians had close contact with their patients and learned of failures of medication by direct questioning. This is in contrast with the situation in large institutions where patients migrate frequently and the follow-up of persons with minor symptoms is difficult.

Ambulatory patients were instructed to drink six glasses of hot water a day, to eat nothing cold in an effort to prevent hyperperistalsis, to take no cathartics or laxatives, and to eat a bland diet. Each patient took one capsule containing 250 mg. of propethyleneoxides three times a day, and reduced the dosage as necessary. If the abdomen became tender the patient was told to report for antibiotic therapy. Mineral oil was not included in the regimen.

Hospitalized patients received a diet similar to that recommended for ambulatory patients. Antibiotics and propethyleneoxides were prescribed and controlled by the physicians in charge.

CLINICAL EXPERIENCE

The patients were grouped according to their presenting symptoms. These were, in order of frequency: 1) changes in bowel habits, 2) obstipation, 3) melena, and 4) local and general peritonitis.

Changes in bowel habits

Patients whose bowel habits had changed were examined carefully, to rule out carcinoma of the colon. A thorough colonic examination with double air contrast and barium radiographic studies was performed, to confirm the presence of diverticulitis. The patients received one capsule containing 250 mg. of propethyleneoxides three times a day until their symptoms disappeared. Thereafter, the dosage was reduced gradually until the bowel movements became normal in consistency and the patient was still able to control them. If the initial large dosage were to be continued, anal incontinence might develop. The patients' acceptance of the medication proved gratifying. Their symptoms disappeared. The diverticula were not propagated by the need for straining during defecation, so that complications from this potentially serious disease were reduced.

Obstipation

Obstipation secondary to low-grade colonic obstruction was considered to be a sign of potential malignany until proved otherwise. Interparietal hernias, such as pelvic prolapse and internal hemorrhoids, were common, and indicated constant straining with increased intra-abdominal pressure. This pressure is likely to cause rupture at the site of these pathologic conditions and thus increase the number of diverticula and their capacity. Malignant obstruction of the left colon

can occur in patients with diverticula. On 2 occasions, we have seen complete obstruction of the sigmoid colon with classic radiographic signs and findings of carcinoma of the left colon. In the course of preparing these patients for a temporary diverting operation, the obstruction was cleared. Subsequently, a barium enema revealed only inflammatory obstruction secondary to diverticulitis. This, we felt, was an indication for radical surgical treatment. While the patients were being prepared for resection of the colon, their symptoms vanished. They refused operation because they were symptom-free. They have remained so to date. One 50-year-old nurse was hospitalized twice for obstruction of the large bowel. She received propethyleneoxides and became symptom-free. She remains so as long as she continues to take this medication; when it is discontinued, the obstipation returns, but relief can again be obtained by the use of propethyleneoxides.

Melena

Melena without hematemesis in persons past 40 years of age (unless preceded by a history of peptic ulcer) was first investigated by means of the sigmoidoscope and a barium enema. We found severe melena in some patients with diverticulitis. The blood was bright red, and there was no bleeding elsewhere. A thorough gastro-intestinal work-up was undertaken in each case. Two patients bled profusely to the point of syncope and surgical shock. The hemoglobin levels were 9.1 Gm. and 8.6 Gm. per 100 ml., and were increased by administering 1500 cc. of whole blood. The medical management described was instituted. Neither patient has had a recurrence during periods of eighteen months and four months, respectively.

We have never seen a patient bleed to death from diverticulitis, and believe that surgery should be reserved for unusual cases of melena secondary to this disease.

Local and general peritonitis

In older patients with diverticulitis, acute abdominal conditions of sudden onset were a diagnostic problem. Laparotomy proved to be the best means of diagnosis. For instance, a transudate that looked like dishwater indicated perforation in the left colon. We were not able to exteriorize this type of perforation but we packed the omentum around the inflamed colon, and started medical treatment of the peritonitis. All patients so treated recovered rapidly from this accident. In a 79-year-old woman, such a perforation occurred while she was straining at stool. She had had an appendectomy, and diverticula had been demonstrated by barium enema four years previously, so she was treated expectantly. She recovered within twenty-four hours. The administration of propethyleneoxides reduced the need for straining and the patient has had no subsequent complications from her numerous diverticula.

A blind study of propethyleneoxides was also conducted at the infirmary, using patients of advanced age. This study continued for two months. No changes in weight were noted, nor were there any side-effects. The patient voluntarily discontinued the use of laxatives.

SUMMARY

The medical treatment of diverticulitis and its complications in the past has been discouraging. A bland diet and antibiotic therapy did not prevent the recurrence of symptoms, and the disease progressed until the onset of obstipation with consequent straining during defecation led to serious complications.

With an increasingly large population of elderly people, the need for successful medical management of this condition is important.

In a study of the use of propethyleneoxides in 300 ambulatory and hospitalized patients, this nonionic wetting agent proved valuable as an adjunct in the medical treatment of diverticulitis. There was a gratifying degree of acceptance by the patients. Symptoms tended to disappear and the need for straining at stool diminished.

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A CONTROLLED CLINICAL EVALUATION OF DEXTRO-PROPOXYPHENE HYDROCHLORIDE PLUS ACETYLSALICYLIC ACID

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The unchallenged prime function of the physician is the study and control of human pain. Often relief of pain must precede accurate diagnosis and definitive therapy. The advent of a non-narcotic, non-toxic synthetic analgesic, therefore, is a matter of no small moment in the annals of the healing art.

This study is concerned with the practical clinical evaluation of dextro-propoxyphene hydrochloride,[1] a new synthetic analgesic (*a*-d-4-dimethylamino-1,2 diphenyl-3 methyl-2 propionoxy butane hydrochloride). The discovery of this compound by Pohland and Sullivan (1) was the culmination of efforts by the National Research Council to promote American independence from foreign control of opium production.

The initial clinical evaluation of dextro-propoxyphene hydrochloride by Gruber and associates (2) demonstrated an effectiveness equal (milligram for milligram) to that of codeine, with the added advantages of fewer gastro-intestinal side-effects and absence of tolerance or physical dependence.

MATERIALS

The materials used in this study consisted of: 1) dextro-propoxyphene hydrochloride (32 mg.) in combination with acetylsalicylic acid (325 mg.); 2) acetylsalicylic acid (325 mg.); and 3) placebo.

All 3 preparations were administered in the form of specially coated tablets,[2] in order to avoid the gastric irritation reported to occur with conventional uncoated acetylsalicylic acid preparations.

METHOD

Effectiveness in controlling pain was determined in 2 groups of patients. In the first group, the outstanding symptom was severe pain from an acute condition—traumatic, inflammatory and otherwise. In the second group, protracted pain arising from chronic disease was the common clinical factor.

For patients less than 60 years of age, 2 of the special coated tablets of dextro-propoxyphene hydrochloride and acetylsalicylic acid (D.P.H. + A.S.A.) were administered every three to seven hours, depending on the duration of analgesia. For older debilitated patients, 1 of the special coated tablets was given every three to six hours. The dosage was doubled when analgesia appeared to be inadequate. The patients' subjective need for additional analgesia was the principal criterion for stepping up the frequency or quantity of the preparation.

In addition to the factor of subjective comfort, results were assayed by the duration of

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[1] Dextro-propoxyphene hydrochloride (Darvon) was supplied by the Lilly Research Laboratories, Indianapolis, Ind.

[2] Special Intestinal Release tablets developed by Lilly Research Laboratories.

comfortable sleep, physical mobility and attitudes or interpersonal relationships in the social environment.

Most of the older patients with long-standing illness associated with chronic pain were drawn from the population of a modern, well-organized nursing home[3] where excellent care and detailed observation were available.

In acutely ill patients having severe pain, D.P.H. + A.S.A. was administered until recovery was complete. Most of this group were ambulatory.

In both groups, when increased dosage (3 to 4 tablets) did not induce adequate relief of pain, other analgesics were substituted and the result was considered a failure. When there was moderate relief, permitting some degree of functioning, results were tabulated as good. Results were considered excellent when there was complete relief of pain.

Initially, the drug combination was administered every five hours, and the interval was either increased or decreased according to the duration of analgesia. The intent was to determine the maximum possible duration of analgesia with the minimum effective dose of the specially coated preparation.

Other supplementary modalities of therapy were either discontinued or brought to an irreducible minimum in order to eliminate extraneous factors which might influence the analgesic effect.

Ambulatory patients were interviewed two or four times weekly, and the hospitalized geriatric patients were examined and questioned daily.

During the course of observation of 12 patients in the chronic disease group, D.P.H. + A.S.A. was discontinued and placebos were given for a period of less than one week, after which D.P.H. + A.S.A. was resumed. In another group of 10 patients, specially coated tablets containing only 325 mg. of A.S.A. were substituted for ten days. Responses to these blind-control substitutions were recorded and evaluated.

Various laboratory studies were made before and during treatment, to determine the possible toxic effects. These studies included urinalysis, hemograms, and series of hepatic and renal tests.

RESULTS

Seventy patients were studied in order to determine the analgesic properties of dextro-propoxyphene hydrochloride plus acetylsalicylic acid. Of these, 38 had acutely painful conditions and 32 had painful chronic diseases. There were 40 females and 30 males. The range of age in 42 patients was from 17 to 59 years, and in 28 patients, from 60 to 84 years. Ninety per cent of the older patients were in the chronic disease group.

The diagnostic distribution of patients is listed in Table 1. The majority of patients in Group I suffered pain from acute traumatic or inflammatory disease. In Group II (chronic illness) the pain arose from degenerative and inflammatory diseases of the joints, vascular disturbances, or the complications of diabetes mellitus.

Analgesia

Analysis of results (Table 2) indicated a general effectiveness of 88.6 per cent—that is, 54.3 per cent of results were *excellent* and 34.3 per cent were *good*. In only 11.4 per cent of patients was relief from pain inadequate.

In both Groups I and II the distributions of the 3 types of relief were approximately alike. Only in the cases of diabetic neuropathy was there a disproportionate degree of failure—50 per cent in the small group of 4 patients with this disease.

[3] Forest Hills Nursing Home, Forest Hills, N. Y.

Data on the duration of relief from pain are listed in Table 3. The average duration of analgesia with the 1-tablet dosage was 4.2 hours, and with the 2-tablet dosage, 5.9 hours. In 4 patients who reported no relief from pain during the 1-tablet regimen, the dosage was doubled.

TABLE 1

Diagnostic Distribution of Patients

Group I Acute Illness		Group II Chronic Illness	
Acute low back syndrome	9	Osteo-arthritis	14
Neuritis, neuralgia	7	Rheumatoid arthritis	7
Myositis and muscle injury	10	Post-CVA contracture	2
Acute joint disturbance (traumatic or inflammatory)	9	Diabetic neuritis	4
Headache	3	Migraine and vascular headache	5
Total	38	Total	32

TABLE 2

Analgesic Effects of Dextro-Propoxyphene Hydrochloride plus Acetylsalicylic Acid in 2 Groups of Patients

	Excellent	Good	Poor
Results in Group I (38 Patients)			
Myositis, muscle injury	6	4	0
Acute low back syndrome	5	3	1
Acute joint disturbance	4	4	1
Neuralgia, neuritis	3	3	1
Headache	2	1	0
Total	20 (52.5%)	15 (39.7%)	3 (7.8%)
Results in Group II (32 Patients)			
Osteo-arthritis	10	3	1
Rheumatoid arthritis	4	2	1
Migraine	2	2	1
Diabetic neuritis	1	1	2
Post-CVA contracture	1	1	0
Total	18 (56.3%)	9 (28.1%)	5 (15.6%)

Totals

Excellent	54.3%
Good	34.3%
Poor	11.4%

TABLE 3
Duration of Relief

Group I 2-Tablet Dosage		Group II 1-Tablet Dosage	
	No. of Patients		*No. of Patients*
2-3 hours	0	2-3 hours	1
3-4 hours	3	3-4 hours	5
4-5 hours	9	4-5 hours	16
5-6 hours	21	5-6 hours	6
6-7 hours	9		
Total	42	Total	28

Control study

Placebo. In 12 patients of Group II, placebos were substituted after a minimum of three weeks of effective relief with continuous administration of D.P.H. + A.S.A. Within twenty-four hours, 10 of the 12 complained of pain. On the second day, the remaining 2 also voiced complaints of discomfort. After the fifth day of placebo administration, D.P.H. + A.S.A. was resumed. There was prompt relief of pain in all 12 patients.

Acetylsalicylic acid alone. In another series of 10 patients from Group II, specially coated tablets of acetylsalicylic acid identical in appearance with the combination tablets, were substituted. Six of these 10 patients complained of pain, and 3 experienced moderate discomfort during the first twenty-four hours after the change. The tenth patient (chronic osteoarthritis) appeared to be equally comfortable with either medication. On the sixth day, the D.P.H. + A.S.A. combination was resumed, and was followed by effective analgesia in all 9 patients who had been complaining of pain.

Side-effects and toxicity

Nausea and/or vomiting occurred in 2 patients who were receiving the 2-tablet dosage, and in 1 who was receiving the 1-tablet dosage of D.P.H. + A.S.A. Constipation occurred in 2 patients (double dosage) and drowsiness in 3 (double dosage). None of these reactions was of sufficient intensity to warrant discontinuance of the medication.

There were no rashes, diarrhea, vertigo or paresthesias. Blood and urine studies showed no toxic effects on the hematopoietic, renal or hepatic systems.

Tolerance and physical dependence

After three months of continuous therapy with D.P.H. + A.S.A., 12 patients from Group II were discharged from the nursing home with no provision to continue the medication. Although there was a recurrence of pain in most of them, in none was there the slightest evidence of withdrawal symptoms such as are observed after withdrawal of a narcotic.

Further, those patients who received D.P.H. + A.S.A. for prolonged periods manifested no evidence of tolerance. At no time was there subjective or objective need for increased amounts of the analgesic to achieve optimum comfort.

SUMMARY AND CONCLUSIONS

Dextro-propoxyphene hydrochloride combined with acetylsalicylic acid was administered orally to 70 patients ranging in age from 17 to 84 years.

It was found to be an effective analgesic. Side-effects were fewer than would be expected from equivalent doses of codeine, and there was no evidence of damage to the hematopoietic, renal or hepatic systems.

Physical dependence and tolerance were not observed in any of the patients.

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PANEL DISCUSSION ON THE MANAGEMENT OF ALLERGIES IN GERIATRIC PATIENTS*

Moderator: JOHN M. SHELDON, M.D. Professor of Internal Medicine, and Director, Department of Post-Graduate Medicine, University of Michigan Medical School, Ann Arbor, Michigan.

Panelists: ROBERT A. COOKE, M.D., Director, Institute of Allergy, Roosevelt Hospital, New York, N. Y.

STANLEY G. HAMPTON, M.D., Assistant Clinical Professor of Medicine, and Director, Allergy Clinic, Washington University School of Medicine, St. Louis, Missouri.

BRAM ROSE, M.D., Associate Professor of Medicine, McGill University, and Associate Physician, Royal Victoria Hospital, Montreal, Canada.

WILLIAM B. SHERMAN, M.D., Associate Clinical Professor of Medicine, Columbia University, College of Physicians and Surgeons, New York, N. Y.

MODERATOR JOHN M. SHELDON: I shall ask the panelists a number of questions relative to the problem of allergy and pertinent to the senior citizens of our country. Because of their importance, we shall attempt to emphasize asthma and conditions of wheezing and dyspnea. We hope, time permitting, to remark upon other allergic manifestations in geriatric patients.

First, I want to ask Dr. Cooke about *the effect of aging upon pre-existing allergic disease, particularly asthma, hay fever, and dermatitis.* What is your view, Dr. Cooke?

DR. ROBERT A. COOKE: When we speak of allergic diseases, we should preface our remarks by saying that, even today, it is almost impossible to express a positive opinion on any phase of allergic phenomena that cannot be disputed. However, I shall try to give what I believe to be the consensus with regard to certain points.

Basically, there is evidence that allergies develop as a result of some hereditarily transmitted capacity, which we speak of in general terms as an "allergic constitution." When we say that, we mean only that persons who acquire allergies have a capacity to react in a way that normal and nonallergic persons do not.

To put it another way, substances with which one comes in contact in any way externally, or by inhalation, ingestion, injection or infection, may react to produce allergic lesions such as asthma, hay fever, dermatitis or urticaria.

The Moderator has asked: "What is the effect of aging upon such diseases?" In infancy, the principal allergies, aside from an occasional acute one due to food, are dermatitis (eczema) and asthma. As eczematous infants grow older, at about 5 years of age or earlier, the eruptions tend to diminish and undergo spontaneous cure. However, because these children have an inherited allergic constitution, asthma and hay fever often develop, with sensitivity to dusts, pollens or animal danders by inhalation or possibly by infection. For the most

* Conducted at the Graduate Symposium on Geriatric Medicine of the American Geriatrics Society and the American Academy of General Practice (Rhode Island and New York Chapters), New York City, November 19 and 20, 1956.

part, they carry this allergy through life, but as they continue aging something new may happen. When they reach the age of 40 or so, infection becomes a major factor in accentuating the symptoms; it may even be a cause, as bacteria can act as allergens. This is known as bacterial allergy.

In cases of asthma which begin in childhood and continue up to about age 40, the basic sensitivity to inhaled substances is combined with the factor of infection. However, asthma which begins after age 40 is likely to represent bacterial allergy, and requires prompt and effective treatment; otherwise, it will continue with gradually increasing severity throughout life. The same is true of vasomotor rhinitis. Although I have seen hay fever from pollen or dust begin as late as age 70, onset at such a late age is unusual. There is something special in the way of an inherited constitutional defect in all allergies. Once started, allergy continues through life, manifesting itself in one form or another. The earlier the cause is discovered and overcome, the less disability there will be. The allergic person may live with his sensitizations, but devoid of symptoms, as long as he has no contact with the sensitizing substances– dusts, foods, drugs or infections.

MODERATOR SHELDON: Thank you, Dr. Cooke. Has any other member of the panel a comment with regard to the effect of aging upon pre-existing allergic disease?

Dr. Hampton, I should like to ask you a specific question. *What is the effect of aging upon the allergenic reaction to a test on the skin?*

DR. STANLEY G. HAMPTON: The reaction to a skin test in the young and the middle-aged adult is rather outstanding. The skin of an aged person does not react to the test as intensively as that of a younger person. There are 2 parts to a positive skin reaction—the wheal and surrounding erythema. In elderly people, the wheal may occur as in younger persons, but the erythema may be much less intense. This tends to support the idea of a triple response as proposed by Lewis: 1) increased permeability of capillaries accounts for the wheal, 2) dilatation of the capillaries accounts for the immediate surrounding erythema, and 3) dilatation of the afferent arterioles accounts for the red flare. Perhaps, because of the less elastic capillaries and arterioles of the aged skin, the second and third phases of the triple response are reduced, thus rendering the skin less reactive.

One piece of investigative work does not seem to confirm this clinical experience. The work was carried out a few years ago at the Washington University School of Medicine by Dr. Michael Schwartz of Denmark when he was in St. Louis on a fellowship. In this study, 110 recipients were used for passive transfer studies with ragweed serum. Equal numbers of the subjects were above and below the age of 50 years (up to age 96). The stronger concentrations of serum produced more wheal reactions in the skin of the older recipients than in the skin of recipients below age 50. However, with dilutions of serum, the skin of the younger persons showed positive reactions in the transfer test when the skin of the older persons failed to do so. The difference was attributed to a poor blood supply wasting away the H-substance which accounts for whealing.

Lewis and Grant reported that a histamine wheal remained longer in the skin of subjects in the upper age group than in the skin of younger persons. Schwartz

quotes Merrill Chase to the effect that a wheal caused by physiologic saline will persist longer in the skin of an older person than in the skin of a younger person. However, the diminution in erythema prevents more accurate interpretation of such observations.

MODERATOR SHELDON: Very good, Dr. Hampton. May I ask you this specific summarizing question? *From the practical viewpoint, is it true that skin tests can be of diagnostic value in asthmatic and in allergic patients, even though the person is old and has senile changes in the skin?*

DR. HAMPTON: Yes—absolutely so.

MODERATOR SHELDON: Have you a comment, Dr. Rose, with relation to skin reactions?

DR. BRAM ROSE: Not at this point.

MODERATOR SHELDON: Dr. Cooke, or Dr. Sherman?

DR. COOKE: I have nothing else to say.

MODERATOR SHELDON: I want to call on Dr. Sherman, and ask him for *the causes of asthma starting in middle age.*

DR. WILLIAM B. SHERMAN: It is important to separate the causes of asthma into primary factors, which create the basic sensitization, and secondary factors, which precipitate attacks in a patient who already has primary asthma. The primary factors are well known—dust inhalation, foods, and occasionally drugs and infections—and may cause asthma at any age. As Dr. Cooke has already mentioned, multiple factors of different types may operate simultaneously in the same patient.

The secondary factors, which cause the asthmatic patient to have attacks at a particular time, include cold, damp weather, irritating odors and fumes, and exertion. Psychic influences are also important. Perhaps we shall discuss them later, but for the time being they can be classified as secondary factors which precipitate attacks in patients predisposed by certain primary factors. Infection must also be taken into account. In certain cases of asthma, infection may be the primary factor. However, in other patients, such as those who have asthma due to inhaled dusts or pollens, an acute respiratory infection can precipitate an asthmatic attack which is due fundamentally to the primary inhalation factor and only secondarily to the infection.

In the younger age group, from the age of 5 to the age of 40 years (omitting infants), probably 90 per cent of the cases of asthma are due to inhaled allergens—pollens, dust, animal dander, feathers, and so on. At about age 40, there is a rather abrupt reversal in the trend. Among new cases of asthma arising after the age of 40, the intrinsic or infective type predominates. Only about 10 per cent of new cases of asthma arising after this age show positive results with skin tests for sensitivity to inhalants, pollens, and a few foods. The other 90 per cent are cases of so-called intrinsic asthma, chiefly representing allergy to infection—although I am not sure that all the members of the panel would agree. In any event, these are not simple cases of asthma in which one can elicit a specific reaction to some external factor and obtain therapeutic results by separating the patient from that factor.

Along with this change in type of asthma with aging, there is a considerable increase in the incidence of asthma due to drugs. Among these drugs, aspirin is outstanding. It causes many more asthmatic reactions than all other such drugs combined. Thus, when we speak of drug asthma, we usually think in terms of aspirin sensitivity. Without doubt, these cases are much more common after age 40 than in younger groups.

I have nothing specific to say about endocrine factors. Perhaps Dr. Rose has some comment on that part of the problem.

DR. ROSE: I would list smoking as one of the secondary factors. I do not believe that smoking is a primary cause of the sensitization which produces asthma. However, there is no doubt that, in the patient susceptible to asthma, tobacco smoke is a secondary irritant that can precipitate attacks or make attacks worse. It probably is an important factor. There is evidence that smoking causes bronchitis rather than true bronchial asthma, although I would classify it as an important secondary factor in the latter.

MODERATOR SHELDON: Dr. Sherman, *do you advise elderly patients with asthma to stop smoking?*

DR. SHERMAN: I often do, but if they show great distress, I do not always insist upon it. If I find anyone smoking more than a pack a day, I certainly advise him to cut down to reasonable limits. I find it very hard to get patients to stop completely. However, some of the enthusiastic ones who have stopped completely have had surprisingly great relief of their asthma.

MODERATOR SHELDON: I should like to ask the other members of the panel their reaction to smoking by persons beyond middle age. Dr. Cooke, what is your reaction?

DR. COOKE: I think it is an important factor in asthma. There is a quantitative element in it. I would draw the line at about half a pack of cigarettes a day. We could almost limit the danger to the inhaling of cigarette smoke; it is more directly irritant than pipe smoking or even cigar smoking, with which there usually is not the same amount of inhalation of smoke. A pack of cigarettes a day can readily induce the congestion and the cough that will precipitate an asthmatic attack. Patients who indulge in excessive smoking, which I would say is above 6 cigarettes a day, have enough irritation to warrant advising them to reduce, if not to eliminate cigarettes. The problem of cutting down smoking is almost as difficult or worse than eliminating it. Smoking is a factor that must be taken into account.

MODERATOR SHELDON: Thank you, Dr. Cooke. Dr. Hampton, any comment? What do you do in this case?

DR. HAMPTON: Let me comment on the remark that Dr. Sherman made about the 10 per cent of older persons with positive skin reactions. I am sure that Dr. Sherman means that 10 per cent will show positive skin reactions to the etiologic factors of the allergic disease. A larger percentage may show positive reactions, but these may be nonspecific and unrelated to the etiology.

Smoking plays a tremendous role. As Dr. Sherman stated, those who stop entirely are frequently quite surprised at the relief.

In Boston, the statement has been made that particles the size of smoke are the etiologic factors in emphysema, whereas larger particles such as dust or pollen are etiologic factors in asthma. I try my best to induce the patient to stop smoking—although not the first time I see him. I try to gain his confidence, see him several times, admit that I am a smoker myself, and finally advise him to discontinue smoking.

MODERATOR SHELDON: Dr. Sherman, have you any rebuttal to Dr. Hampton's remarks with regard to the skin test?

DR. SHERMAN: My figure of 10 per cent was intended to refer to actual causative factors proved by the results of treatment. Dr. Hampton might obtain a skin reaction in a higher percentage of cases, but I doubt whether in more than 10 per cent one can show by treatment that asthma is due to the substance giving rise to the skin reaction.

DR. COOKE: We ought to emphasize that what Dr. Sherman was talking about was cases of asthma that began after the age of 40 years, in which the percentage was not high. The carry-over from the younger group would make it considerably higher. In asthma that begins after age 40, the element of sensitization factors as found in the younger group is much less. I definitely agree with him, but it should be emphasized that he was speaking of asthma that begins after age 40, not that carried over from earlier life.

MODERATOR SHELDON: Dr. Rose, have you a comment about smoking?

DR. ROSE: I was going to say that, if the opinions of the panelists were inversely related to the square root of the volume of smoke that is going forth from this table at the moment, it would be quite clear that what they have said belies their actual thoughts, because no one gives a hoot whether he is smoking or not.

MODERATOR SHELDON: Don't do what I do, but what I say. Is that it? The question was brought up as to the relation of smoking to bronchitis. I should like to ask, *How you differentiate true asthma and chronic bronchitis?* Dr. Rose.

DR. ROSE: Differentiation between the extremes of the 2 conditions, namely, chronic obstructive pulmonary emphysema and bronchial asthma in the older patient, is relatively simple. With intermediate cases, the problem becomes somewhat more difficult.

Clinically, the history is first in importance. Asthma is characterized by paroxysmal attacks, which usually occur when the patient is at rest. In the person who has frequent attacks, they will be precipitated by emotion, exertion, cold air, and other secondary factors, as Dr. Sherman has mentioned. On the other hand, unless emphysema has progressed until the patient is breathless at rest, the dyspnea is usually related to some form of exertion or to an acute infection, so that it is important to find out what precipitates the attack of dyspnea.

The second point is that a person with emphysema will usually tell you that, when he is not too breathless, he can sleep in bed, lying flat and using 1 pillow. As the disease progresses, he may be forced to use more than 1 or 2 pillows, but this does not happen as frequently as in the person with asthma. With the onset of asthma and true bronchial wheezing—I call it bronchial spasm; Dr. Cooke

likes to call it bronchial obstruction—the victim usually requires 2, and sometimes 3 pillows, even though there may be no cardiac involvement. This is not a crucial differentiating factor, but it is helpful at times.

The family history must be taken into consideration. Most persons with true obstructive pulmonary emphysema have no family history of allergy, whereas a fair proportion of those with asthma do.

A person with advanced emphysema usually has the characteristic barrel chest with an increased antero-posterior diameter, and a flattened diaphragm. To say that this is not seen in cases of asthma is not true, but barreling is far less apparent in the latter condition. The emphysema patient, during moderate to acute attacks, is often cyanotic. The asthma patient is rarely cyanotic unless there is acute status asthmaticus.

In cases of emphysema, there is frequently evidence of right-sided cardiac involvement with increased venous distention. I do not believe, although some members of this panel will disagree with me, that asthma leads to emphysema. The heart sounds are not of great diagnostic importance, but in the patient with emphysema the second pulmonary sound will often be more accentuated than in the normal person. This is rarely observed in the patient with asthma.

The degree of relief obtained with different types of medication also helps to establish the nature of the attack.

A few biochemical changes occur in emphysema that are not commonly found in asthma, namely, an elevated CO_2 content and moderate lowering of the pH of the blood. This is not a great help in evaluating an office case clinically, but it is important with regard to the type of treatment. This is particularly true when determining the amount of oxygen that should be given to a patient admitted to the hospital with acute dyspnea, in whom the differentiation between asthma and emphysema is uncertain.

Finally, there is a point with reference to the sputum. If the patient has asthma, at some time or other the sputum may contain mucoid spirals. These are, so far as I know, never found in emphysema. Beyond that, I would not like to go. Even if one uses complicated pulmonary function tests, there is little to differentiate the patient with obstructive pulmonary emphysema from the patient with reversible emphysema associated with an acute prolonged attack of asthma.

MODERATOR SHELDON: Thank you, very much. Would any other member of the panel care to comment?

DR. HAMPTON: I want to challenge Dr. Rose's statement that asthma does not lead to pulmonary emphysema. The high incidence of pulmonary emphysema in what is known as infective or intrinsic asthma, furnishes statistical evidence that the cough of asthma leads to emphysema. Whether or not asthma leads to emphysema, the *cough* of asthma leads to emphysema, just as the cough of tuberculosis and the cough of chronic bronchitis lead to it. Pulmonary emphysema may also be seen in the younger age groups, even in children and in those of teen age who have had asthma since early life.

I know that it does not come within the scope of this discussion to enlarge

upon the reasoning as to whether or not asthma leads to emphysema, but I should like to challenge Dr. Rose on this statement. No doubt he has some well founded investigative work to substantiate it. To me, it is always amazing to see the inconsistency with which pulmonary emphysema develops in the asthmatic patient. There seems to be some sort of predilection. A person may have asthma for a long time and yet not have pulmonary emphysema, whereas a person who has had asthma for a shorter time may soon suffer from intractable and severe pulmonary emphysema in addition.

MODERATOR SHELDON: Dr. Cooke, any comment?

DR. COOKE: I think that blocking caused by intrabronchial obstruction is an important factor in producing distention of the lung, which is really what emphysema is. There is so much evidence of it in the asthmatic patient that we must consider the relationship between asthma and the obstruction. Either difficult breathing or coughing tends to promote distention of the alveoli and, therefore, the development of that condition in the lung.

MODERATOR SHELDON: Dr. Rose, I should like to give you time for rebuttal.

DR. ROSE: Thank you, Dr. Sheldon. We have been interested in the problem of the cause of obstructive pulmonary emphysema, particularly with relation to bronchospasm. A number of years ago, we studied such a group by means of cardiac catheterization. We chose persons who looked as though they should have emphysema, whose diaphragms were low, and whose lungs were hyperaerated during attacks. We catheterized their hearts. In contradistinction to persons with true obstructive pulmonary emphysema, there was no pulmonary hypertension. When a moderate degree was induced, it was purely secondary to intrapulmonary changes, that is, changes within the thorax itself.

In asthma, during the expiratory phase the blood pressure is elevated, and during the inspiratory phase it falls to normal. This is not true of emphysema. I could continue at great length, but in view of the friendship that exists between me and my friends at this table, with whom I heartily disagree, I shall desist.

MODERATOR SHELDON: Thank you, Dr. Rose. I should like to have Dr. Cooke comment about asthma and its relation to the production of emphysema, being a bit more inclusive.

DR. COOKE: It seems to me that this has developed into a question as to what is emphysema, and what is not.

The general consensus is that the term emphysema means distention of the alveoli throughout the lungs. It seems paradoxical to talk about obstructive emphysema when obstruction is exactly what exists in the asthmatic patient. The basis for asthma is an obstruction in the bronchi, caused largely by thickenint of the bronchial wall and by the very curious and tenacious mucoid plugs. There may also be an element of bronchial spasm. I do not agree entirely that asthma and bronchospasm are synonomous, because there is little evidence for a greater degree of spasm in emphysema than in asthma, or vice versa.

The degree of bronchial obstruction depends entirely upon the age of the patient and the duration of the asthma. We see children who are particularly resistant to therapy and have prolonged asthmatic attacks, defying all present

medical procedures. Children may have asthma at age 8 or even earlier, and be continuously asthmatic for years. All the evidences of asthmatic obstruction may develop, including the barrel chest and even a moderate degree of right-sided cardiac enlargement. The point is that from time to time these children have not only their chronic asthmatic condition, but more. In those who have short and periodic attacks of asthma, dilatation of the alveoli occurs to some extent. If they are relieved, the process is reversible. It is reversible because the tissues are young and have retained their elasticity. In the older age group, however, tissues have begun to undergo change. We speak of it as atrophy. It affects not only the lung, but the skin, the muscles and all other tissues, so that there is loss of vitality and elasticity. In cases of persistent and prolonged dyspnea due to asthma, we see this marked type of distention, *i.e.*, emphysema by roentgenographic and clinical evidence has developed into an important factor. The elderly have passed the age when emphysema will disappear, even if the asthmatic factor is relieved. The tissues have lost the capacity to return to their normal or original state.

In addition to emphysema in these cases, there is an altogether different process, namely, pulmonary fibrosis. The evidence of fibrosis during life is chiefly indirect—in roentgenograms of the chest. Fibrosis is difficult to demonstrate directly, other than at necropsy. The marked increase in pulmonary shadows, the accentuation of the bronchial markings, and other changes throughout the lung are seen in these prolonged cases. The fibrosis is secondary to infection. That is one of the reasons why we see more of it in older people than in children. However, children with prolonged asthmatic conditions resistant to medication may have not only emphysema but also pulmonary fibrosis. In such cases, there is always evidence of infection, whether primary or secondary.

The development of fibrosis is really the end-result of infection in the bronchi and glands; it is possibly secondary to sinus involvement, which accentuates it. Fibrosis is a part of the picture induced not only by obstruction (emphysema) but by the infection which is an important feature in prolonged cases. When there is obstruction in the bronchial tree, there must be dilatation of the alveoli as a result of the dyspneic respiratory effort and coughing. This is my concept of emphysema. Emphysema is reversible when the attacks are occasional or periodic as in youth, and irreversible when the condition is prolonged.

MODERATOR SHELDON: Thank you, Dr. Cooke.

I should like to ask Dr. Sherman a question, which I hope will define what we are coming to in relation to the management of asthma. *What things, other than those already discussed, would you have in mind when you see a patient who is short of breath and wheezing?*

DR. SHERMAN: In dealing with middle-aged patients, more care must be exercised in making the diagnosis of asthma. In children and young adults, bronchial asthma is by far the most common cause of wheezing and periodic dyspnea. In older people, one must also take into account the possibility of organic obstructions, of tumors either inside the bronchi or pressing on the bronchi, of pulmonary fibrosis due to silicosis or other pulmonary disease, and a

great many other factors. How does one differentiate these? It can be done by resisting the tendency to conclude that the patient has bronchial asthma, by taking a careful history, by performing a careful physical examination (noting particularly if the signs and symptoms are localized in one lung or one part of a lung), and by examining the sputum for the features characteristic of asthma. For instance, if the sputum is bloody, there is reason to suspect a lesion inside the bronchi. Perhaps most important is roentgenographic examination of the chest. Obviously, every patient with asthma should have a roentgenogram of the chest as a part of his examination. It becomes even more important in dealing with middle-aged and elderly patients. Most of the lesions to which I have referred can be recognized by means of careful roentgenographic examination of the chest.

A test which may help to differentiate organic obstructions from asthma, is the effect of epinephrine upon the wheezing. If epinephrine produces rapid and striking relief, the more likely diagnosis is asthma. If epinephrine does not produce relief, one has to think more seriously of other conditions. Bronchoscopy is a valuable procedure when in doubt; only thus can some of these problems be settled.

Another aspect is the differentiation of cardiac asthma or cardiac dystonia from bronchial asthma. Again, this is much more difficult in elderly patients than in young patients. In the latter, asthma is usually due to extrinsic factors. It is likely to be acute, periodic, and of the bronchial type. Heart disease in young patients is usually valvular, and relatively easy to diagnose if the heart is carefully examined. In older patients, asthma is not so characteristically periodic It tends to be of the chronic, low-grade variety. Heart disease in older patents is more often of the arterial type. There are no characteristic murmurs, so it is not as easily recognized. It is important to remember that both arteriosclerotic heart disease and asthma are exceedingly common in this older age group. Therefore, the patient frequently has both conditions. It becomes not so much a question of differential diagnosis as of studying the patient carefully from both aspects and not jumping to the conclusion that, because he has arteriosclerotic heart disease, he does not have bronchial asthma as well.

We shall not have time to discuss the different methods for diagnosis of arteriosclerotic heart disease. It should be emphasized, however, that in the older age group, it is common to have asthma and heart disease in the same patient. These diseases must be treated simultaneously, but separately.

MODERATOR SHELDON: Thank you, Dr. Sherman. Does any other member of the panel wish to comment?

Dr. Sherman told us of bronchoscopy as a diagnostic procedure. I should like to comment in a positive way relative to bronchoscopy and the instillation of contrast media into the bronchus, and see if the panel agrees or disagrees with me. To my way of thinking, these procedures offer a valuable diagnostic aid, but therapeutically they are disappointing. I suspect that the instillation of oils does harm rather than good. Does anyone on the panel disagree with me?

Let us proceed, then, to the therapy of elderly persons with asthma. We

try to define it by indirection. I shall call upon Dr. Cooke first, and ask him *how he would manage an elderly patient with bronchial asthma.*

DR. COOKE: Dr. Sheldon asked this question as though the diagnosis of asthma had been made. When these patients present themselves, and before we start to do anything in the way of management, we have to make a diagnosis. Perhaps the patient has been referred with a history of asthmatic attacks. It is our function to decide whether the disease is asthma or not. That has just been discussed by Dr. Sherman.

The next step is to ask ourselves: "If this is an asthmatic condition characteristic of the middle-aged or elderly, what is the cause?" One cannot manage any patient properly and satisfactorily without a clear-cut conception of the cause of the difficulty. Therefore, a careful study must first be made. This involves the past history, particularly with regard to familial allergic disease. Has the patient inherited an allergic constitution? Has he at any time exhibited evidence of sensitization to anything, or has he suffered from some disturbance such as drug sensitivity, that is not a factor in the present condition. Such a patient will probably be found to have the capacity to become allergic to certain things, such as drugs. For example, in many patients who are sensitive to aspirin, asthma is often the chief, and sometimes the sole, evidence of their sensitization.

How did the condition develop? Was the onset rapid or gradual, and what were the circumstances? Was he at home? Environmental factors are always important in these cases, in addition to certain other intrinsic factors.

After a careful history, it is necessary to make a careful and full physical examination. Once this is done, and you have concluded that the disease is asthma, it is your task to carry out the various procedures that will not only confirm this conclusion but contribute toward determining the cause. The status of the heart and the kidneys, and the general physical condition must be determined. Laboratory tests of various sorts should be made. Roentgenographic examination in asthmatic patients of this age group should include the sinuses. The possibility of dental infection should receive particular attention. For instance, if there is infection in the upper molar areas, it is likely to have spread to the maxillary antrum, and the antrum infection may clear up after the removal of the diseased tooth.

Having made these studies, skin tests should be undertaken in all cases, because they help to throw light upon certain factors. Not all positive results are significant, so careful clinical correlation is important. It is of no particular moment that a man with chronic asthma is allergic to some food that he eats only once or twice a year (for example, mushrooms). A positive reaction to, or a history of being sensitive to, mushrooms does not solve his immediate problem. He has a chronic condition. It takes continuous contact with a causative factor to maintain his allergic manifestations. Having determined the possible causes by means of careful clinical observation, the physician may remove the patient from his environment and place him where he does not have to come in contact with the offending allergen, for example, the dust in the factory, office, or home.

If the patient is symptom-free in one place but not in another, the external environmental factors can be sought. Though careful clinical observations and trials must be made in order to satisfy the requirements, that does not mean the performance of the hundreds of available skin tests. A clear-cut idea of the nature of the trouble can be obtained by a screening method, involving perhaps half a dozen of the more important inhalant allergens. Foods can be covered by 10 or 12 food tests.

It is characteristic of allergic disease that rarely is there a single cause. Multiple sensitization is the rule rather than the exception, and persons who have an allergic disease are likely to be sensitive to 3 or 4 things. Infection should not be overlooked. I hope Dr. Sheldon will bring it up as a factor, and mention what may be done about it.

One must decide whether or not a respiratory-tract infection is present, and whether or not there has been removal of nasal polypi. Has there ever been evidence of true sinusitis? These conditions, confirmed by roentgenographic examination, are important factors in preparation for management. The patient is treated symptomatically while we are making serious efforts to discover the cause. Without a fair conception of the cause, one cannot manage these cases properly.

MODERATOR SHELDON: Thank you, Dr. Cooke. We shall come back to the question of the management of infection. I should like, now, to ask various members of the panel what specific medications may be used in the asthmatic patient, not only during the acute attack, but in the prevention of future attacks.

First, I am going to ask Dr. Hampton *whether or not iodides are of any value in the treatment of asthma, and when they are indicated.*

DR. HAMPTON: Expectorants are important agents in symptomatic therapy for the treatment even of mild cases of asthma and emphysema. In the patient with severe asthma, expectorants probably head the list, as far as symptomatic therapy is concerned. An expectorant is just as valuable, if not more so, as the so-called bronchodilators and agents used to reduce bronchial edema, such as ACTH and steroids. The literature contains many necropsy reports showing that death from asthma is due to anoxia resulting from extensive bronchial mucus. Therefore, expectorants are of prime importance, particularly in the patient acutely ill with asthma.

Iodides are of great value as expectorants, that is, potassium iodide by mouth and sodium iodide intravenously. Time does permit a discussion of the pros and cons of the pharmacologic effect of iodides. There is some evidence that the action is not directly on the bronchi, but a reflex pathway in the stomach; if so, this would rule out intravenous iodides as effective agents. Other investigators, however, have obtained contrary results. When the patient is extremely ill, intravenous iodides are very effective in addition to oral iodides in large doses. Iodides should not be given intravenously until they have first been given orally in order to determine possible sensitivity.

Lobelia, an old herb now almost discarded, is an effective expectorant. Then

I would list ammonium chloride, glycyrrhiza, and glycerine. Thus, there are other expectorants to substitute for iodides, if the patient should prove to be iodide sensitive.

In treating acute attacks of asthma, intravenous iodides will blend with other preparations, such as ACTH and theophylline. In St. Louis, we call this combination an intravenous cocktail. Iodides should be forced, as they dissolve the sticky mucus which can cause death in cases of asthma.

MODERATOR SHELDON: Does any member of the panel disagree with Dr. Hampton, or wish to add anything with regard to expectorants? If not, I should like to consider the next subject—*the so-called bronchial dilators*, and ask Dr. Sherman to speak about them.

DR. SHERMAN: Bronchial dilators are, in a sense, the "backbone" of the treatment of bronchial asthma, which is primarily a matter of obstruction of the smaller bronchi and bronchioles.

Two groups of drugs are useful in this regard—the epinephrine group and the xanthines, among which aminophylline is the primary drug. The epinephrine group includes adrenaline and many related products. The most important ones are epinephrine itself, and ephedrine for the immediate treatment of the acute asthmatic attack. Epinephrine is still the first drug to try, and usually the most effective. It has the disadvantage that it is not potent when taken by mouth, so that it is less useful for treatment of the patient at home. However, it is effective by inhalation as an aerosol. There are many types of epinephrine products for inhalation, all of which are essentially similar and valuable in relieving mild attacks of asthma.

For oral treatment, ephedrine is the primary agent and probably does everything that any of the other drugs of the group will do. It provides effective relief for relatively mild asthma, and can be used in the home because it is taken orally.

Ephedrine may be combined with other drugs, such as mild sedatives. As ephedrine is somewhat stimulating, these combinations are more practical and effective than ephedrine alone. It is easy to adjust the amount of ephedrine and of sedative in capsule form for a particular patient so that he will not be stimulated by the drug to the point of interference with sleep, but neither will he have so much sedative as to become sleepy in the daytime.

Of the other drugs in this group, we need mention only one, isopropylarterenol, which is more familiar under the trade names of Isuprel and Norisodrine. It is as effective as epinephrine when administered by aerosol inhalation or inhaled as a powder.

Among the xanthines, aminophylline is valuable and is the most commonly used. If epinephrine does not relieve the acute attack, the next drug to try is aminophylline, intravenously. It is so potent that it must be injected very slowly, taking five or ten minutes to administer the whole intravenous dose. If the patient is in the hospital, it is often preferable to dilute the dose with 100 or 200 cc. of dextrose and give it by intravenous drip, in order to control the rate of administration.

By mouth, aminophylline and the other xanthines are irritating and likely to cause nausea and vomiting when given in doses large enough to control severe asthma. They are most useful in combination with ephedrine and sedatives.

Aminophylline is effective by rectum, and therefore is useful for home treatment of the patient who has an attack not easily relieved by aerosol inhalation or by ephedrine orally. Aminophylline may be given in a rectal suppository or dissolved in a retention enema. It provides effective and practical home treatment.

MODERATOR SHELDON: Thank you, Dr. Sherman. *What dose of epinephrine is indicated in an asthmatic patient?*

DR. SHERMAN: That is a very good point. The dose is exceedingly variable. For that reason I would suggest a modest dose initially, perhaps 0.4 cc. of 1:1000 solution. One should wait five or ten minutes to see if the patient obtains relief. There should be no hesitation in repeating the same dose in five or ten minutes, if necessary. It is so hard to judge the correct dose, that it is much better to give a small dose (with the idea that a second one may be necessary in ten minutes) than to attempt to guess the total requirement at first.

When we give what I call a relatively large dose—1 cc. of 1:1000 solution—it does less good than it should, because the local constricting effect of epinephrine interferes with its absorption. Two small doses have a better effect than one large one.

MODERATOR SHELDON: *Are there any contraindications to the use of epinephrine in this case?*

DR. SHERMAN: I can think of nothing that would stop me from trying epinephrine in a patient having a severe, acute asthmatic attack. Even if the patient were hypertensive or known to have heart disease, I would not hesitate to give him a slightly reduced dose—0.3 cc. of 1:1000 solution—watching him carefully, and repeating the dose in five or ten minutes.

We may worry about the presence of hypertension and heart disease, but asthma has such an adverse effect upon both of these conditions that, when epinephrine relieves the asthma, we have helped the patient a great deal more by giving this drug than by worrying about the contraindications.

MODERATOR SHELDON: I agree with you. There might be one rare instance—I can hardly visualize it being a problem that will confront anyone—wherein fear of giving epinephrine might arise. That is in the person receiving chloroform anesthesia. However, if the patient is under anesthesia, one is not going to be worried about asthma anyway.

Does any member of the panel disagree with this statement? It is important to remember that there really are no primary contraindications to the administration of epinephrine.

DR. COOKE: Might it not be well to emphasize the fact that, when a patient with hypertension is given a dose of epinephrine and the blood pressure reading is taken again in ten or fifteen minutes, it will have dropped rather than increased as a result of the epinephrine. The effort to breathe increases the pressure and is a large factor in producing the degree of tension that one finds

at the instant. In a patient with severe dyspnea the blood pressure may be increased; the relief obtained rapidly with epinephrine induces lowering.

MODERATOR SHELDON: Thank you, Dr. Cooke.

Now, I should like to start a discussion on some compounds that are tremendously interesting and valuable in the treatment of middle-aged and elderly asthmatic patients. I shall call upon Dr. Rose to give us his views on *the use and abuse of, and indications and contraindications for, corticotropin and corticosteroids.*

DR. ROSE: This group of compounds undoubtedly constitutes one of the most useful groups of drugs for the treatment of asthma, as well as other conditions in the older patient.

The question is often asked: "Which substance should one use?" "Would you use corticotropin in preference to cortisone or the other steroids? If so, why?" The first question that one has to answer is, "Are there any real contraindications?"

The first consideration has to do with the status of the patient. Has he been bedridden? If so, how much osteoporosis does he have? Fortunately, among asthmatics the incidence of osteoporosis with spontaneous fracture of a vertebra is much lower than in patients with arthritis, for example. I have seen it in only 1 case of asthma.

Secondly, "Is diabetes present? If so, is it a contraindication to corticosteroid therapy?" In my experience, it is not.

A history of mental depression is a factor to be considered. I know that these points have been belabored many times, but they are important. So are the questions, "Does the patient have any tendency toward heartburn? Is there a history of ulcer? Is cardiac failure present? If so, does that modify your choice of compound?"

I think there are no significant contraindications to corticosteroid therapy so long as one is aware of the possible side-effects and adopts methods of preventing their occurrence. Corticosteroids are best used in self-limiting diseases, such as seasonal hay fever or asthma, when one knows that they will be given for only a short time.

Does the adrenal of the older person respond as rapidly and as well to a dose of corticotropin as does that of the young, robust person? We know from studies on steroid excretion that both urinary 17-ketosteroids and glucocorticoids are reduced to some extent in elderly persons. It is not known whether this change is controlled by the adrenal or by the pituitary gland.

It does not much matter which corticosteroid you use, as long as you give an adequate dose. Because of the ease of administering the oral corticosteroids, we use them in preference to preparations of ACTH. There is also the possibility that ACTH, given in a dose of 20 units by intravenous drip, may induce sensitization.

With reference to the excretion of adrenal steroids in the urine, one additional feature might be mentioned. We have found that in most older asthmatic pa-

tients the level of steroid excretion is considerably lower than in nonasthmatic patients of the same age. Apparently the adrenal is less capable of responding to ACTH than in normal persons.

The most recent oral steroids are by far the best—prednisone and prednisolone. They do not affect the electrolyte balance nearly so much as the older compounds. Dependent edema does not develop. When there is any possibility of the presence of a cardiac disorder, these are the steroids of choice.

We like to start with a sufficient dosage, depending upon the severity of the illness, and then decrease it to a maintenance level. The maintenance dosage will vary considerably. In some older persons, it will be at the surprisingly low level of 5 mg. of prednisone once a day, and in some instances, once every second day. Higher dosages are sometimes indicated. It is better to start at a high level and lower it than to start at a low level and wonder when a remission will commence. Failure to respond may be due to intercurrent infection. This must always be kept in mind.

If a patient has been maintained with prednisone, what is the advantage of giving him adrenocorticotropin as a booster, in the form of one of the new zinc preparations? In my experience there is none. If you give prednisone, both the adrenal and the pituitary will be suppressed. Then one wonders whether or not something should be done to maintain the integrity of the adrenal cortex. Why not give 2 or 3 injections of corticotropin (ACTH)? The reason for not doing so is this: Prednisone suppresses the adrenal cortex for a much longer period of time than following administration of other oral steroids including hydrocortisone and cortisone—even as long as six months. Thus, when a person, who has received prednisone and then been maintained by other means, is given corticotropin within one to three months after prednisone has been discontinued, the adrenal probably cannot be stimulated. A longer interval after omission of prednisone is required. Even if one succeeds in stimulating the adrenal, the injections of ACTH depress the pituitary further. Oral adrenal steroid therapy is reinstated, and before long one is back to the starting point. What good will have been done? As far as I can see, none, except to have satisfied yourself that you have done what is said to be the best thing. Because I do not know whether it is the best thing or not, I do not resort to so-called booster injections of corticotropin at intervals of six months, a year, or any other time.

Other standard types of therapy should be used in controlling asthma when the patient is receiving prednisone or some other steroid. By so doing, the amount of steroid necessary will be decreased, the likelihood of ultimate discontinuation of steroids will be increased, and the patient will save money.

MODERATOR SHELDON: On the question I asked, you could spend a full hour and not cover the subject completely. I should like to clarify a few things, if I may, Dr. Rose. You mentioned that, initially, patients should receive a relatively high dosage of a corticosteroid. You stated that your choice might be prednisone. *Assuming that the patient is elderly, what do you mean by high dosage?*

DR. ROSE: It depends upon the status of the patient. For example, if asthma

of a troublesome degree has not responded to bronchial dilators or expectorants, 20 to 40 mg. of prednisone daily for two days will probably prove adequate. The dosage can soon be reduced.

If a patient with acute asthma receives initially a daily dosage of 20 or 30 mg., he will not respond for five or six days. On the other hand, if he is given 80 mg. in fractional doses the first day, and 60 mg. the second day, he will improve within thirty-six to forty-eight hours. The dosage can then be reduced rapidly to a level commensurate with the severity of the disease. This plan saves time for the patient, and time and worry for the physician.

MODERATOR SHELDON: Thank you. Now I should like to ask you 2 more questions.

What would persuade you to administer a corticosteroid to an asthmatic patient? Obviously, not all asthmatic patients receive steroids initially.

DR. ROSE: Dr. Sheldon, I assume that everything else has been tried. Let us suppose that the patient has been to you, and has not done well. Then he has gone to Dr. Sherman, or Dr. Hampton, and he has done a bit better, but not as well as he ought. Finally, he has been seen by Dr. Cooke, who has tried all possible therapeutic measures. I am sure that Dr. Cooke would treat such a patient with steroids.

I start steroid therapy only when a patient is acutely ill and requires immediate relief not obtainable by other means, or when the patient has been a chronic invalid for a number of years and has not responded to conventional forms of therapy. This point should be emphasized—as we have learned from our experience during the past six years, when we have had ample opportunity to study these patients both in the wards and in the clinic. The whole aspect of the clinic has changed. Prior to the advent of steroids, we had a large indigent clientele. Many were unable to work, and unable to support themselves. Our therapy, obviously, was not good enough. Now, many of them receive steroids in low dosages, under continual watchful supervision. We are vigilant concerning the onset of such things as tuberculosis and other infections, or whatever may arise. Many of the patients are employed in the hospital. Those who are not, are able to take a job outside and support their families. They can afford to pay for their medication, whereas, previously, they could not.

MODERATOR SHELDON: *Would you elect to use corticosteroids in case of status asthmaticus of several days' duration in a patient who had not received corticotropin or corticosteroids before you saw him?*

DR. ROSE: Yes, I certainly would. I can see no contraindication.

MODERATOR SHELDON: *Would you use corticosteroids in preference to intravenous corticotropin?*

DR. ROSE: That would depend largely upon whether or not the patient had recently been receiving oral steroids. If the patient had had corticotropin previously and a rapid result was desired, ACTH could be given by slow intravenous drip along with intramuscular injections of the long-acting zinc preparation in a dosage or 20 to 30 units twice daily until a response was obtained. On the other hand, if the patient had, as recently as one month or six weeks previously,

been receiving an oral steroid for a considerable length of time, the treatment of choice would be high doses of corticosteroid orally.

MODERATOR SHELDON: *How often do you think that a patient receiving chronic corticosteroid therapy should be seen by his physician?*

DR. ROSE: The plan that we follow is this: Patients receiving routine therapy (that is, a maintenance dosage of 5 or 10 mg. of Meticorten per day) report by telephone, or come to the clinic or the office at least once every two weeks. They do not have to come as long as they feel well and as long as nothing bothers them. We insist upon seeing them regularly each year at intervals of five to six months in order to re-evaluate their status, and to make sure that no unwanted side-effects are developing.

MODERATOR SHELDON: You have alluded to the various complications that may follow prolonged corticosteroid therapy. What have you observed that was troublesome? *What are some of the common complications of prolonged corticosteroid therapy?*

DR. ROSE: The majority of patients have little trouble. Some, however, become susceptible to infection. This can be troublesome and must be dealt with appropriately.

Three patients in our series, which is a large one, have osteoporosis with spontaneous fractures. Two of them have the rare combination of asthma and advanced arthritis.

Other than that, Dr. Sheldon, I would say that there have been no serious consequences. We have had only 1 case of perforated ulcer, and that was in a patient with periarteritis nodosa. There have been some cases of gastric distress, which was readily controlled with an antacid or an anticholinergic drug along with an appropriate diet.

Acute collapse may occur in the presence of infection in a patient who has recently stopped steroid medication. This is due in part to suppression of the pituitary-adrenal mechanism, and it requires rapid and heroic measures.

MODERATOR SHELDON: *Do you keep your patients under the so-called Albright regimen, if they are receiving corticosteroids for a prolonged period?*

DR. ROSE: It depends largely upon the type of person. If he is robust and active, one generally has little to fear with reference to the development of osteoporosis. It is only in sedentary or bedridden persons that this need be considered. Even then, I do not know whether Albright's regimen will prevent marked osteoporosis. We do not know just what metabolic mechanism is involved in this loss of calcium and protein which results in decalcification of bone.

We add testosterone to the treatment program, particularly in the older age group, if we think it is indicated. To some patients, we give supplementary calcium.

MODERATOR SHELDON: *Dr. Rose, are you concerned if your patient comes to operation after prolonged corticosteroid therapy? If so, do you take any precautions with regard to surgical procedures?*

DR. ROSE: Any patient, who receives steroid therapy for any length of time, is warned that he must always tell any physician he may consult that he has been

taking steroids. We have been able to follow those of our patients who have undergone operations—for instance, thyroidectomy, appendectomy, or even an abdominal perineal resection, which is an extensive procedure. We have lost only 1 patient among 15 or 20 undergoing a major operation.[1]

MODERATOR SHELDON: Thank you very much. We could go on and on, but I should like to give the other members of the panel an opportunity either to agree or disagree with Dr. Rose and to add any comments of importance that they care to make.

First I shall call on Dr. Cooke.

DR. COOKE: I am sure that Dr. Rose mentioned this. We should always attempt, in patient receiving corticosteroids for asthma, to deal with the causative factor. We should not see patients, make a diagnosis of asthma, and resort to this type of therapy for their immediate relief without at the same time making a serious effort to find the cause. If there is infection, continuous antibiotic therapy or chemotherapy should be instituted. The patient may belong to a group for whom nothing else can be done, but we must always try to find the causative factor and treat it at the same time that the patient receives continuous therapy for relief of symptoms.

MODERATOR SHELDON: Thank you, Dr. Cooke. Dr. Sherman?

DR. SHERMAN: I think that the subject has been covered.

MODERATOR SHELDON: Dr. Hampton?

DR. HAMPTON: In our study in St. Louis, continuous infusions of ACTH for twenty-four to ninety-six hours resulted in a much greater excretion of 17-ketosteroids than intermittent eight-hour daily infusions of the same dose of ACTH. Moreover, although a single injection of 40 units of ACTH-gel led to very little increase in the 24-hour excretion of 17-ketosteroids, the excretion after four days of ACTH-gel approached that associated with daily eight-hour infusions of regular ACTH. The newer corticosteroids, such as Meticorten, approach the clinical effectiveness of ACTH-gel.

I should like to ask Dr. Rose 2 questions. He stated that steroids used for maintenance therapy may depress the activity of the adrenal cortex for periods up to six months. He also mentioned that ACTH suppresses the pituitary. Will the suppressive effect of ACTH last as long as that of steroids? What is your experience when comparing prednisone with prednisolone? We have found that prednisone and prednisolone are equivalent in clinical effect, although there are situations in which prednisone may be slightly more effective than prednisolone, and vice versa.

DR. ROSE: I cannot answer the first question, and I know of no work that would answer it reasonably. I agree with Dr. Hampton that, clinically, there is no difference between the therapeutic effects of prednisone and prednisolone.

MODERATOR SHELDON: Thank you very much.

We have much material to cover and want to allow a few minutes at the end

[1] Our routine procedure is to give 200 mg. of cortisone or equivalent per twenty-four hours in fractional doses on the day before, the day of, and the day following operation, after which the dose is slowly reduced.

for audience participation. Therefore, I am going to ask several questions and request that they be answered briefly. Dr. Hampton, will you please speak of *the use of oxygen and aerosols.*

DR. HAMPTON: Although oxygen is necessary for life, it is a two-edged sword. The administration of 100 per cent oxygen by mask, or even by intranasal tube, may be dangerous. In a case of severe asthma, the physician should stand by and watch the patient for signs of carbon dioxide narcosis, at least when oxygen therapy is initiated.

Aerosols have their place. They serve as sputum solvents and bronchodilators, particularly in combination with intermittent positive pressure breathing as supplied by the Bennett and the Emerson IPPB respirators. There is controversy over the matter of whether a bronchodilator substance, such as epinephrine or isopropylarterenol, may be just as effective when administered as an ordinary aerosol as by intermittent pressure breathing. Motley (who introduced IPPB), Segal and his associates, Smart and his co-workers, and others including ourselves have found that 100 per cent oxygen can be administered with intermittent pressure breathing without increasing CO_2 narcosis. A practical bronchodilator-sputum solvent for use in the nebulizer of the intermittent pressure apparatus would be 0.5 cc. of isopropylarterenol 1:200 diluted with 5 cc. of a detergent such as Alevaire or Tergimist.

The same materials may be given as ordinary aerosols by using compressed air as the force. Even pressure produced by a bicycle pump will do. A hand nebulizer may be used for spot relief. The latter has its place, provided the patient does not use it every fifteen minutes or so when he is obviously refractory to its effect because of the mucus in the smaller bronchi.

MODERATOR SHELDON: Thank you. *Do you agree with the statement that, to date, enzymes such as trypsin are hazardous to use as aerosols in elderly asthmatic patients?*

DR. HAMPTON: They may be hazardous. Crystalline trypsin (Tryptar) may be used in selected cases, but it is highly irritating and should not be used in the concentration ordinarily advised (125,000 units). Concentrations of 50,000 units diluted in 3 cc. of diluent, given every six to twelve hours for a limited number of treatments (3 to 6) is a safer dosage schedule. Desoxyribonuclease (pancreatic dornase) is less irritating and, like trypsin, may be a useful therapeutic tool, particularly when the sputum is purulent.

MODERATOR SHELDON: I should like to know whether you agree or disagree on one other question. *Is it not true that oxygen is a potent anti-expectorant, and that in its use one risks promoting further bronchial plugging?*

DR. HAMPTON: I pass.

MODERATOR SHELDON: Has anyone else a comment to make concerning oxygen or aerosols?

If not, let me ask Dr. Sherman to give his view as to *the use of antihistamines in asthmatic patients.*

DR. SHERMAN: Antihistamines are vastly overrated as treatment for asthma. Many asthmatic patients who have been treated by general practitioners rely

on an antihistamine as their main treatment. Often, they do not obtain worthwhile results. A few mild cases of asthma may be relieved by antihistamines, but only the mildest cases, and even these would be better relieved by oral ephedrine or aminophylline. The only indication for the use of an antihistamine is in the patient who is made uncomfortable by the side-effects of ephedrine. I would always combine the antihistamine with aminophylline in order to obtain the additional benefit of aminophylline. I would not rely on an antihistamine as the primary drug to relieve acute asthma.

MODERATOR SHELDON: Does the panel agree? I should like to proceed to the next point, which I think is important, and that is, *the use of fluids in hospital patients*. Dr. Cooke.

DR. COOKE: This would apply to cases of severe asthma. At the time of hospital admission many patients have had severe dyspnea for a number of days. They are greatly dehydrated. The mere act of breathing eliminates a great deal of water. Under such conditions, the patient may not want to take fluids by mouth. Therefore, it is important to treat these patients with intravenous fluids, on an emergency basis. This provides an opportunity to give not only corticotropin, but aminophylline and glucose as well.

The use of intravenous fluids in severe cases of asthma is an important part of treatment, particularly when there is an element of dehydration. Dehydration tends to increase inspissation of the bronchial plugs, so that breathing becomes more difficult.

In severe cases, it is important to pay some attention to diet and supplementary medications. Many patients suffer from abdominal distention. They may have taken drugs to stop coughing, and have become severely constipated. The bowels may not move for several days, resulting in distention with pressure on the diaphragm, which adds to the asthmatic difficulties. Therefore, when these patients are first admitted it is our practice to give them nothing but fluids for a day or two—by mouth, as soon as possible. Proper attention is also given to clearing the bowel with cathartics, with colonic irrigations, or with enemas in order to lessen intra-abdominal pressure. This is important.

MODERATOR SHELDON: Thank you, Dr. Cooke.

I should like to ask Dr. Hampton to give briefly his experience and state *whether tranquilizers and sedatives are useful in asthma*.

DR. HAMPTON: Briefly, yes. Sedation is important in asthma. The patient has anxiety because he cannot get his breath. Actually, he cannot get his breath out, but he thinks he cannot get it in. For years, barbiturates and other sedatives have been used.

The new tranquilizing drugs, according to my short experience, have a definite place as adjuncts in the management of asthma in the aged as well as in younger persons. The hospitalized patient with severe acute asthma needs a certain amount of sedation, although not enough to depress the respiratory center. Morphine cannot be used. My favorites are, first, chloral hydrate either orally or rectally (the capsule can be punctured with a pin for rectal use), and second, paraldehyde orally or rectally. Rectal administration of paraldehyde does not

keep the odor from the room, since this drug is excreted through the respiratory tract. Equal parts of ether and olive oil rectally can be used to put the patient to sleep. As Dr. Sheldon mentioned a minute ago, when the patient is receiving an anesthetic, one usually does not have to worry about asthma. Large doses of barbiturates must be used with caution. Whereas morphine is contraindicated, Demerol is worth consideration in selected cases, *e.g.*, when the patient cannot tolerate other sedatives, or if they have been ineffective.

MODERATOR SHELDON: Dr. Rose, will you make a brief statement with regard *to gamma globulin and antibiotic and chemotherapeutic agents.*

DR. ROSE: The effect of gamma globulin in increasing the resistance of allergic patients is not established. The rationale does not seem to be clear. The antibodies involved in the production of the cases of true extrinsic asthma are found in the gamma globulin fraction. Gamma globulin is innocuous, if one wants to give it. It is not a sensitizing agent, as it is native to human beings.

The subject of antibiotics and chemotherapeutic agents is a big one. Briefly, there are 3: the sufonamides, bactericidal agents, and bacteriostatic agents. The best bactericidal agent is penicillin; unfortunately it may sensitize the patients, so it should not be used if one can help it. It should never be instilled into an antrum, given as a lozenge, or put on the skin. It is least innocuous when given by mouth. The usual blood levels obtained are adequate to control most infections.

Any one of the newer bacteriostatic agents can be used. Despite initial adverse reports, we still believe that chloramphenicol is one of the most effective.

MODERATOR SHELDON: Thank you. I should like to emphasize at this point that, when any medication is given to a patient, there is the risk of an allergic response. Dr. Sherman alluded to the subject in relation to aspirin, and Dr. Rose alluded to it in relation to penicillin. Any other medication that might be given to an elderly asthmatic patient is also capable of producing allergic shock, asthma, skin eruptions, and even death. Therefore, it is extremely important to take a careful history before any medication is given to an allergic patient (this would apply to any person). It takes only one minute to ask the patient whether or not he has had the drug you wish to prescribe; and if he has had it, whether or not any symptoms resulted from its administration. If there were symptoms, it is unwise to use that particular medication, or one from a closely related group of drugs.

I had in mind asking, unbeknown to the speakers, a number of other questions to complete the picture as we see it in asthmatic patients. However, our chairman allotted us an hour and forty-five minutes. In the time left, I should like to ask for questions from the floor, and then to summarize what we have attempted to cover.

Are there any questions from the floor?

SPEAKER: I am Dr. Salteforis, a Public Health Officer in Sweden.

This is about the cause of asthma. I should like the opinion of the panelists. During the past two years, I have had several cases of bronchial asthma, and among them 2 cases of status asthmaticus immediately following shock. The

shock was caused by a traffic accident. The patients were 2 middle-aged women, 60 or 65 years old. (From the point of view of geriatrics, I consider that middle age.) We had no past history, and nothing relevant to assist in finding the explanation.

I would be interested to know whether, in America, you think that shock could be the cause of asthma. Could a relation be found between the two clinically?

MODERATOR SHELDON: I believe the question is: *Do the panelists believe that shock can be the trigger mechanism in inducing status asthmaticus?* Dr. Cooke?

DR. COOKE: I have never seen a case like those cited by our friend from Sweden. I suppose it is possible. We have always thought that shock might be a factor in the precipitation of an attack in those who have previously had asthmatic manifestations. That it might be the cause of a true asthmatic condition would perhaps be open to question. I would say that these persons had the dyspnea characteristic of an asthmatic attack. Whether or not it could properly be called asthma is debatable, because I did not understand the basis for the diagnosis of asthma. However, this occurrence is outside of my experience. I have never seen anything happen as promptly as that.

MODERATOR SHELDON: Are there any other comments from the members of the panel?

SPEAKER: *Should breathing exercises or diaphragmatic belts be used?*

MODERATOR SHELDON: A question is asked about breathing exercises and the use of emphysema belts. This has been popularized and used extensively in England. I shall attempt to answer the question from my own experience.

Theoretically, it should be very effective. From the practical standpoint, it is difficult to have a patient carry through breathing exercises effectively. Our results have been poor. For that reason, I have yet to see any measurable evidence—if one is to use pulmonary function tests as a guide—that belts and breathing exercises produce improvement in symptoms.

Some patients have said that they felt better after using a belt, or breathing exercises, but there was no change in their pulmonary function.

Another question?

SPEAKER: (A question is asked with regard to the *cost of ACTH preparations.*)

MODERATOR SHELDON: Will some member of the panel answer the question with regard to the cost of ACTH preparations.

DR. ROSE: A question arises as to the difference in cost of the various ACTH preparations. The first reason is that, if a manufacturer can get more for his product, he obviously will do so. The second reason is that, until recently, disagreement existed among manufacturers as to the unitage, which is now standard. As I understand it, all preparations should cost approximately the same.

MODERATOR SHELDON: In other words, you are paying on the basis of unitage whether you buy for four dollars or for eight.

Another question?

SPEAKER: (Question inaudible.)

MODERATOR SHELDON: Dr. Hampton, will you answer the question.

DR. HAMPTON: The question concerned *the speed of injection of aminophylline.* It is of foremost importance to avoid a generalized vasomotor collapse. When aminophylline is given by syringe, one should administer only 1 cc. per minute until a dose of 250 mg. in 10 cc., or 500 mg. in 20 cc., is given. An intravenous drip with glucose can be used. Slow administration is better in the long run, although less rapid in its action. The glucose may have a synergistic effect on the aminophylline.

MODERATOR SHELDON: I should like to take one minute to *summarize.* I hope that I speak for the panel. What I have heard today suggests that, in general, the management of the elderly asthmatic patient has many problems in common with the management of other allergic patients. There are certain peculiarities in these patients after the age of 40 years, in addition to sensitivity, for which there is no specific treatment. Infection plays an important role.

When an asthmatic patient undergoes a procedure that may cause shock (*e.g.*, a surgical operation) and he has received corticosteroids or corticotropin within the preceding six months, he should again receive corticosteroids, preferably starting twenty-four hours before operation and continuing through the first few postoperative days.

In the elderly asthmatic patient, a factor not present in young persons may be added. That is the factor of retirement and of incapacity. I had expected to cover this particular phase with the panel, but can now only briefly mention the importance of having the elderly asthmatic patient occupied in some way.

Psychosomatic factors are a problem in all asthmatics, and particularly in elderly subjects.

A number of medications can be used, and used safely. The panel has attempted to discuss them in the order of their choice.

Abstracts of Current Literature

THE RELATIONSHIP OF HYPERTHYROIDISM AND PARKINSONISM.

Bartels, E. C., and Rohart, R. R. *A.M.A. Arch. Int. Med.* **101:** 562 (March) 1958.

Because the areas of the brain affected by parkinsonism and by hyperthyroidism are adjacent to each other, a pathologic process in one of them may conceivably cause changes in the other. The simultaneous occurrence of the 2 diseases has been found infrequently, but if hyperthyroidism were suspected in each case of parkinsonism, this coincidence might be found more often. The 2 primary problems with regard to diagnosis are, first, the detection of hyperthyroidism in a patient with parkinsonism which occurs chiefly in older patients with insignificant or no thyroid enlargement, and second, determining whether an adenomatous goiter in a patient with parkinsonism is producing hyperthyroidism. As for treatment, the patient with parkinsonism may deteriorate rapidly if primary hyperthyroidism is not detected. The presence or absence of hyperthyroidism will be the basis for a decision as to whether or not to remove an adenomatous goiter from an elderly patient with parkinsonism. When the 2 diseases exist simultaneously, the signs and symptoms of parkinsonism are likely to predominate, so that it is difficult to discover hyperthyroidism. Although many of the signs and symptoms of the 2 diseases are the same, a few differences may give a clue to diagnosis. For example, the tremor in parkinsonism is coarse and irregular, whereas the tremor of hyperthyroidism is fine and rhythmical. Features of hyperthyroidism that may become manifest despite the predominantly parkinsonian features are 1) hyperorexia, 2) the fine, velvety smooth, warm moist skin characteristic of hyperthyroidism, and 3) severe muscle wasting, which can be demonstrated by tests of muscle strength (in parkinsonism the power of muscle contraction is not lost; the "paralysis" refers to slowness of movement). The radioactive iodine uptake of the thyroid gland and the determination of the serum protein-bound iodine level may be helpful in establishing the diagnosis of hyperthyroidism in the presence of parkinsonism, but both are subject to change by factors other than hyperthyroidism. Determination of the basal metabolic rate with the use of thiopental anesthesia has served as a useful decisive diagnostic procedure in questionable cases. Twelve cases of hyperthyroidism associated with parkinsonism were found in a 10-year period at The Lahey Clinic, where the admissions for hyperthyroidism average 300 per year. Four cases that are presented illustrate the difficulties in diagnosis.

TUBERCULIN SKIN SENSITIVITY IN OLD AGE.

Beresford, O. D. *Am. Rev. Tuberculosis* **77:** 323 (Feb.) 1958.

The tuberculin skin sensitivity of 1,012 people more than 65 years old was tested and the results showed a high proportion of negative reactors to 100 TU of Old Tuberculin. Chest roentgenograms of these negative reactors showed that in 29 per cent there was roentgenographic evidence of previous infection with tuberculosis. Further evidence of previous infection with tuberculosis was provided by the use of a Depot Tuberculin which produced a reaction in most of the nonreactors to 100 TU. The suggestion is made that routine tuberculin testing of the aged should be carried out in contact examination, and the advisability of giving small doses of BCG should be borne in mind. (Author's summary)

LE TRAITEMENT DU "SYNDROME MALIN" DES MALADIES INFECTIEUSES (THE TREATMENT OF "MALIGNANT SYNDROME" IN INFECTIOUS DISEASES).

Bickel, G. *Med. et hyg.* (Switz.) **15:** 551, 1957; through Ciba Literature Review **3:** 102, 1958.

If a "malignant syndrome" develops in the course of an infectious disease, corticosteroids often bring about an astonishing turn for the better. It is important to combine the hormone with appropriate antibacterial therapy. Bickel prefers to use prednisone in an initial daily dose of 40 to 80 mg., with subsequent reductions in the amount. The aim is, on the one hand, to utilize the anti-inflammatory effect of the hormone: hyperergic reactions, which—as they "overshoot"—may have an unfavorable effect on the course of the disease, are often eliminated. On the other hand, corticosteroids act as replacements when the adrenal cortex is exhausted, and they promote detoxification. It also appears that in many infectious diseases micro-organisms become, under the influence of corticosteroids, more sensitive to the effect of antibiotics. Adrenocortical hormones, in combination with antibiotics, are primarily indicated 1) in infectious diseases associated with considerable formation of toxin, *e.g.*, malignant diphtheria, 2) when the adrenal cortex is inhibited or even largely destroyed (*e.g.*, Waterhouse-Friderichsen syndrome), and 3) when an infectious disease is in a hyperergic phase characterized by the predominance of mesenchymal tissue reactions to the extent that the organism is threatened more by its own "overshooting" reactions than by the pathogen.

THE COMBINED USE OF A TRANQUILIZER, SYMPATHOMIMETIC, AND VITAMINS IN THE TREATMENT OF ELDERLY PSYCHOTIC PATIENTS.

Blackman, L. H.; Glenn, A., and Olinger, L. *Am. J. Psychiat.* **114:** 837 (March) 1958.

Vita Respital, a liquid preparation containing in each teaspoonful a therapeutic vitamin formula with 0.25 mg. of reserpine and 2.5 mg. of *d*-amphetamine sulfate, was administered three times daily for ten weeks to 73 elderly psychotic patients (aged 47 to 95 years) while 67 similar patients received placebo medication. A double-blind technic was used. The diagnoses among the 140 patients were: senile psychosis, 71; psychosis with cerebral arteriosclerosis, 28; dementia praecox, 10; manic depressive psychosis, 6; involutional psychosis, 19; psychosis due to syphilis, 3; alcoholic psychosis, 2; post-traumatic psychosis, 1. All patients had a poor prognosis. In contrast to the control group, treated patients showed greater degrees of improvement in nutrition, sphincter control, muscle strength, sociability, cooperation, activity, initiative, self-care and appearance. No side-effects appeared and little fluctuation in blood pressure. The ingredients of Vita Respital appeared to exert a synergistic action. This preparation should be of value not only in elderly psychotic patients but in geriatric patients less severely ill than those in this study.

AN ANALYSIS OF CHANGES IN THE SPATIAL VECTORCARDIOGRAM WITH AGING.

Burch, G. E.; Golden, L. H., and Cronvich, J. A. *Am. Heart J.* **55:** 582 (Apr.) 1958.

The spatial vectorcardiograms of 223 normal subjects (159 men and 64 women) between the ages of 20 and 68 years were analyzed in an attempt to determine changes attributable to aging. In most instances, the direction of inscription of the QRSsÊ loops was clockwise in the frontal plane projection and counterclockwise in the left sagittal plane projection. The maximal posterior deflection of the QRSsÊ loops in the left sagittal plane projection was approximately the same in all groups except the oldest, in which it was of smaller magnitude. The incidence of irregular contour of the QRSsÊ loop was found to increase directly with each decade of life of the subjects: 22.5 per cent in the third, 29.3 per cent in

the fourth, 52.8 per cent in the fifth, and 67.7 per cent in the sixth. The distortions involved all portions of the loop. The configuration and spatial orientation of the loops became altered despite the absence of clinical evidence of cardiac disease or detectable alterations in the conventionally recorded electrocardiogram. The reasons for these changes are not known. Myocardial changes resulting in alterations in the time course of depolarization were thought to be the cause, but extracardiac changes with age, such as emphysema and anatomic displacement and rotation of the heart, also may have contributed. The distortions in the spatial vectorcardiogram may serve as an index of significant cardiac changes associated with aging. Whether certain distortions can forewarn of manifestations of serious disease remains to be investigated.

THE USE OF NUCLEIC ACID IN AGED PATIENTS WITH MEMORY IMPAIRMENT.

Cameron, D. E. *Am. J. Psychiat.* **114:** 943 (Apr.) 1958.

Over a two-year period, studies were carried out on the effect of desoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in 23 elderly patients with impairment of the retention phase of memory. Both were prepared in 10 per cent solution and injected slowly intravenously. The initial dose varied from 100 to 500 mg. Up to 4 Gm. of DNA, and up to 2 Gm. of RNA, were given daily. The effects of the drugs were usually noted within four to five days. It usually was not necessary to continue injections for longer than two weeks. Some favorable reaction was noted in all patients, the results being considered good in half of them. Patients with severe memory defects and marked confusion responded best. In most of them, confusion cleared, orientation returned, and retention was restored partially or completely. In cases with partial improvement in memory deficit, further administration of nucleic acid had no further effect. A temperature rise and occasional pain at the side of injection were the only side-effects noted. RNA in capsules was tried orally in average daily amounts of 10 to 20 Gm., with a maximum of 75 Gm. Only limited responses were obtained by this route and gastro-intestinal disturbances occurred in a few patients.

USE OF DIOCTYL SODIUM SULFOSUCCINATE IN CARDIOVASCULAR DISEASE. CORRECTION OF BOWEL FUNCTION.

Dennison, A. D., Jr. *Am. J. Cardiol.* **1:** 400 (March) 1958.

Dioctyl sodium sulfosuccinate, a fecal softening agent which has been used for constipation in various types of patients, offers to cardiac patients the advantages of lack of laxative action, maintenance of a soft fecal mass during the period of bowel inactivity, elimination of the tendency to impaction and the danger of straining at stool, and absence of interference with body water balance. Dioctyl sodium sulfosuccinate was used in a dosage of 240 mg. daily through the period of hospital stay in 103 patients with acute myocardial infarction due to coronary occlusion, pulmonary emboli resulting in pulmonary infarction, cardiac decompensation, and other cardiovascular conditions. The results were uniformly excellent—impaction and straining were avoided and the need for laxatives and enemas reduced almost to nil. The stools remained soft and evacuation was accomplished with ease. In a few patients who received antibiotics, the consistency of the stool also was soft and no loose, watery evacuations occurred.

CHRONIC REFRACTORY MOUTH DISORDERS IN THE AGED.

Epsteen, C. M. *M. Clin. North America* (March) 1958, p. 481.

An elderly patient complaining for any length of time of a sore mouth or burning tongue should have at least a complete differential blood count and urinalysis in order to detect whether or not these symptoms are caused by such disorders as pernicious anemia, leukemia, syphilis or diabetes. The presence of miliary gumma is an indication for a complete serologic survey. In any case, thorough consideration of complaints is indicated. Among the more

common is *burning tongue*. When the underlying factor is systemic, local lesions will usually be found, especially in sprue, pernicious anemia, the Plummer-Vinson syndrome, and nutritional deficiencies. When it is local, dentures, because of their fit or composition, are likely to be the cause. Burning tongue and *stomatitis* also may be caused by a vitamin deficiency—of nicotinic acid, riboflavin, folic acid or pyridoxine, or a combination of these. Because an older person is likely to restrict his diet, a multiple vitamin combination taken twice daily with an extra dosage of the deficient vitamin is recommended. *Geographic tongue*, also called "wandering rash," may appear on one side of the tongue, and shortly thereafter on the other. The lesions commence as small patches which coalesce into one area, the pattern of which resembles a map. A milk-of-magnesia mouth wash and tranquilizers are the only therapy. *Scrotal tongue* with its deep fissures is harmless. *Uremic stomatitis* occurs as a manifestation of severe chronic uremic nephritis. Local treatment consists of aniline dyes for the ulceration and 0.5 per cent HCl as mouth wash to neutralize the ammonia in the saliva. *Senile elastosis*, a degenerative change in the elastic fibers of the skin or mucosa, may be seen on the lips especially in cases of leukoplakia, lupus erythematosus and radiation stomatitis. Other changes in the oral cavity in old age include the absence of stippling of the gingiva and oral tissues, loss of elasticity and resiliency of the tissues, the secretion of thick ropy saliva with a high mucin content, decreased flow of saliva accompanied by a lessened amount of ptyalin, increased susceptibility to infection and trauma, and atrophy of the tongue (which becomes subject to irritation). Black *hairy tongue* may develop following the use of antibiotics, especially as troches, lozenges or powders. *Torus palatinus* is rarely of consequence but may become an obsession with the patient. *Cancerophobia* can be dispelled by the statement that the patient does not have carcinoma, once examination has revealed no organic disease. Processes that affect the jaw are *osteoarthritis*, for which the only treatment is palliative, and *changes in the angles of the mandible* as a result of a loss in the normal intermaxillary space or the vertical dimensions of the normal dental relationship. These result in pain in the region of the joints, catarrhal deafness, and neuralgia of the tongue, pharynx, and head.

EFFECT IN MAN OF LARGE DOSES OF PYRIDOXINE ON SERUM CHOLESTEROL.
Failey, R. B., Jr. *Circulation Research* **6:** 203 (March) 1958.

Twenty-one hospital patients, 5 of whom were elderly diabetic women and 16 of whom were males 41 to 80 years old with chronic pulmonary and cardiac diseases, were given 400 mg. of pyridoxine daily. A significant fall in the serum cholesterol level occurred in the diabetic patients who received the medication for a maximum of seven days. In 10 nondiabetic patients who received the drug for seven days, there was no significant fall in the serum cholesterol level. However, when 6 nondiabetic patients received pyridoxine for thirty-six days, a significant fall occurred and the rise thereafter was delayed and did not reach the original control level. Reasons why the fall in serum cholesterol concentration in this study was no greater may have been due to 1) the "normal" mean serum cholesterol concentration prior to medication, 2) the fact that the patients were hospitalized rather than ambulatory, since the serum cholesterol levels in ambulatory patients appear to be higher, or 3) to the short duration of the study. If pyridoxine were combined with other agents, it might prove more effective.

THE ROLE OF ATARAXICS IN CARDIOLOGY.
Friedlander, H. S. *Am. J. Cardiol.* **1:** 395 (March) 1958.

In the majority of patients seen by a cardiologist, anxiety prolongs and intensifies the physical disorder. That its control by ataractic drugs contributes to a better prognosis for the patient was demonstrated through the use of meprobamate in 41 patients, as follows: coronary thrombosis, 12; coronary insufficiency, 12; labile essential hypertension, 14 (8 were menopausal women and 6 extremely obese men); severe cardiac neurosis, 3. From an initial dosage of 400 mg. of meprobamate three or four times a day, the amount was grad-

ually reduced and the drug was eventually discontinued as the patients lost their nervous tension and became responsive to specific therapy which was given in conjunction with meprobamate. The duration of treatment was from two months to one year; some patients are still receiving the drug in small, widely spaced doses. Drowsiness in a few patients at the beginning of therapy was the only side-effect. It is concluded that the drug is well suited for prolonged administration in chronic disorders with emotional complications. Ataractic medication prevents the patient with a coronary thrombosis or coronary insufficiency from becoming heart conscious. It also dispels the fears of patients with no organic lesion but with a cardiac neurosis. The dosage of coronary vasodilators may sometimes be reduced or eliminated. In essential hypertension, a fall in blood pressure occurs once the calming effect of the drug can be achieved. The elimination of nervous tension in the menopausal patient with hypertension can be accomplished with ataractic drugs. Their effect in obese patients with hypertension enables these persons to adjust to dietary restrictions.

CONSIDERAZIONI DERIVATE DALLA MEDICAZIONE ANTIBIOTICA ENDOBRONCHIAL GUIDATA NEL TRATTAMENTO DELLE CAVERNE TUBERCOLARI (INTRABRONCHIAL ADMINISTRATION OF ANTIBIOTICS IN THE TREATMENT OF BRONCHIAL TUBERCULOSIS).

Giachi, R., and Martinotti, G. *Minerva med.* (Italy) **49:** 293, 1958; through Ciba Literature Review **3:** 109, 1958.

The local, intrabronchial administration of tuberculostatics is better able to bring about the regression or recovery of tuberculous processes than is systemic use of these drugs. Intrabronchial therapy is particularly valuable in cases of primary bronchial tuberculosis. In addition, it is eminently suitable for cavities which involve the bronchus to a considerable extent. Once the bronchial segment has become patent again, chemotherapeutic agents can be introduced into the cavities, thus substantially promoting their healing. In the affected branch of the bronchial tree, the attempt is made first of all to reduce congestion and local edema by introducing Privine, epinephrine, or the like. The patients reported were given streptomycin or viomycin by intrabronchial instillation. Thus, the drug reached the focus of infection in a higher concentration than with other types of administration. The dosage was 0.5 Gm. of viomycin or 1 Gm. of streptomycin once a week initially, and later twice a week. The duration of therapy depended upon the clinical course. Eleven of 26 patients were cured, and 1 improved. In the remaining patients, no success with regard to cure was expected because of the severity of the disease, but in most of them the severe bronchitis was alleviated.

THE EFFECT ON THE CORONARY ARTERIES OF A NEW SUSTAINED ACTION VASODILATOR.

Hirshleifer, I. *Angiology* **9:** 31 (Feb.) 1958.

Twenty-three patients with angina pectoris and electrocardiographic changes characteristic of coronary insufficiency, with and without evidence of old myocardial infarction, were treated with 80 mg. of Peritrate (pentaerythritol tetranitrate) in the form of sustained-action tablets. The clinical effect of this long-acting vasodilator preparation lasts for approximately twelve hours. Each patient received 1 tablet before breakfast and before the evening meal. The period of treatment varied from two to eight weeks. In 14 patients, excellent control of anginal attacks was secured. Exercise tolerance was increased and the need for nitroglycerine reduced. As anxiety lessened, the cycle of anxiety, angina pectoris, nitroglycerine, and further anxiety, was broken. Of the 3 patients who responded only moderately well, 1 with cor pulmonale did not respond as well to nitroglycerine. The other 2 had old myocardial infarctions and ventricular aneurysms. Three unresponsive patients also did not respond to nitroglycerine. Increased gastric motility may have accounted for the poor response in 2 others. The only side-effect was epigastric distress in 1 patient, which did not necessitate withdrawal of the drug. Peritrate sustained-action tablets are valuable

in patients with angina, as they afford reassurance of freedom from attacks and thus permit the patient to lead a more normal life.

COEXISTENT LEUKEMIA AND DIABETES MELLITUS.

Kaufman, R. E. *Am. Pract. & Digest Treat.* **9:** 413 (March) 1958.

A case of coexistent diabetes mellitus and chronic myeloid leukemia in a 65-year-old woman is reported. The diabetes improved concomitantly with the improvement in leukemia produced by radiation therapy to the spleen. Ultimately no insulin was required. It is conjectured that the diabetes may have been caused by leukemic infiltrations into the pancreas or liver and that x-ray therapy directed to the spleen probably caused enough irradiation of the pancreas and liver to destroy them, resulting in improvement in the diabetes. The leukemia became active a second time and required radiation therapy but the diabetes did not recur.

OSTEOPOROTIC KYPHOSIS WITH PARAPLEGIA.

Kempinsky, W. H.; Morgan, P. P., and Boniface, W. R. *Neurology* **8:** 181 (March) 1958.

Two cases of paraplegia due to deformity of the vertebral column as a result of osteoporosis are reported. This role of osteoporosis has not previously been emphasized, as a review of the literature on bone diseases and deformities that may cause spinal cord compression shows. A prolonged menopausal state may have been a contributing factor to the disease in the first patient. Senility contributed in each. Prolonged dietary inadequacy played a part in the osteoporosis in the second patient; the restricted distribution of the fractures indicated unrecognized trauma as a causative factor. The second case might formerly have been diagnosed as Kümmel's disease. It may be that the earlier lack of recognition of a relation between osteoporosis and spinal cord compression may have resulted from the confusing role played by Kümmel's disease. It is now considered to be nonexistent. The administration of testosterone and estrogenic hormone serves a dual purpose in patients such as those described, in augmenting the nitrogen, calcium and phosphorus metabolism in osteoporosis and in the reversal of the accelerated nitrogenous catabolism in acute paraplegia.

SERUM GLUTAMIC OXALOACETIC TRANSAMINASE, LACTIC DEHYDROGENASE, AND GLUTAMIC PYRUVIC TRANSAMINASE ACTIVITY IN EVALUATION OF HEART MUSCLE DAMAGE.

LaDue, J. S. *Am. J. Cardiol.* **1:** 308 (March) 1958.

Serum glutamic oxaloacetic transaminase (SGO-T), serum lactic dehydrogenase (SLD), and serum glutamic pyruvic transaminase (SGP-T) activity in the absence of acute damage of heart or skeletal muscle or of liver has been found to be within normal limits in the following types of disease: infectious, degenerative, neoplastic, toxic, allergic, reactive, and metabolic. Each kind of activity rises within twelve hours and persists as long as six days after acute transmural myocardial infarction. The height and duration of elevation of SGO-T, SLD, and SGP-T are roughly proportional to the size of infarction. Angina pectoris or coronary insufficiency is not associated with a rise in these values unless, presumably, accompanied by heart muscle cell damage. Rheumatic fever with active carditis is frequently associated with concomitant increases in SGO-T activity. The erythrocyte sedimentation rate rises within twelve to twenty-four hours after acute myocardial infarction and may remain elevated for as long as seven weeks. Unfortunately, this modality also becomes abnormal in coronary insufficiency without infarction. C-reactive protein is elevated in nearly 100 per cent of patients after the third day of acute myocardial infarction and remains elevated for as long as three to seven weeks. The blood fibrinogen level reacts similarly. All of these nonspecific phase reactants, including the ESR, the CRP and fibrinogen, are markedly elevated following many infectious disease processes, neoplastic dis-

eases, gout, some gastro-intestinal disorders, pulmonary infarctions, arthritis, and acute rheumatic fever, to mention a few. Therefore, changes in the phase reactants must be carefully evaluated when used as a diagnostic aid for acute myocardial infarction. (From author's conclusions.)

INTRAMUSCULAR TRYPSIN IN TREATMENT OF ACUTE THROMBOPHLEBITIS.
Shafer, F. *Antibiotic Med.* **5:** 104 (Feb.) 1958.

Crystalline trypsin, 2.5 mg. in 0.5 ml. of sesame oil, was given twice daily by deep intramuscular injection to 7 patients with acute, and 3 with chronic thrombophlebitis, whose ages were between 45 and 78 years (average 60.5 years). Five patients of average age 68, with arteriosclerosis complicated by diabetes mellitus, were treated similarly. The duration of treatment varied from five days to two and a half weeks. Acute thrombophlebitis responded with rapid subsidence of inflammation, control of pain within two days, and complete clearing of induration within five days. In the majority of cases, the thrombus disappeared Less satisfactory results were obtained in 1 chronic case of thrombophlebitis, and treatment failed in 2 others. Oscillometric readings of the lower extremities used in the patients with arteriosclerosis complicated by diabetes indicated no improvement after ten days of treatment. Case histories are presented for 5 patients. As a result of these observations, it is thought that trypsin is useful in the treatment of acute inflammatory conditions.

DIFFERENTIAL APPROACHES TO RECENT "MOOD" THERAPY IN THE AGED.
Smigel, J. O. *Internat. Rec. Med.* **171:** 146 (March) 1958.

Individualization of patient care offers the best chance of success in the treatment of emotional disturbances in aging and elderly persons. In addition to somatic and physiologic factors, environmental, situational and social-societal factors must be considered. There is no indication for therapy with ataractic drugs *en masse*. Anxiety, fear, confusion, disorientation, abusiveness, agitation and depression are the principal symptoms. Which type of mood-altering drug promises best to alleviate or eliminate each kind of symptom? Which will give long-term human normalcy? Once anxiety has been overcome, which drug maintains longest a state of calm? What weight should be given to side-actions? Medications that oxygenate cerebral tissue possess the greatest potential for returning a patient to societal and socio-economic usefulness. They avoid the docile existence and lack of acuity engendered by some ataractic drugs. Pentylenetetrazol, which improves the tone of brain tissue through increased oxygen and glucose utilization, offers greater permanence in mood control than do ataractic drugs. It has the advantage of remaining effective when once found so for any patient. The combination of pentylenetetrazol with reserpine or chlorpromazine has permitted an early change to pentylenetetrazol alone, with concomitant lessening of the danger of toxic manifestations from these 2 drugs. Chlorpromazine combines with pentylenetetrazol with greater safety and effectiveness than does reserpine. A study over a four-year period of the use of various drugs to alter moods and emotional states in 355 elderly patients showed that meprobamate has a short period of benefit in altering anxiety symptoms. Its effect on fear is marked. Both uses are marred by the fact that it destroys the will to make decisive choices. Its effect may decline, but is renewed by a period of rest. Meprobamate has little effect upon disorientation and confusion. Rauwolfia preparations have a positive effect upon disorientation and confusion when hypertension is an etiologic factor and cerebral arteriosclerotic changes predominate. It presumably is effective by means of its hypotensive action with the relief of cerebral congestion. Reserpine also allays anxiety, but patients show a detached attitude with relation to their symptoms. In older patients, reserpine loses its potency in ameliorating anxiety and fear and in its hypotensive action—usually not before six months and more likely after a year or so. Anxiety alone or accompanied by agitation or depression is well controlled by pentylenetetrazol. Patients with anxiety or depression alone, from a study of 42 patients given this drug, appeared to respond more readily than did agitated patients. A satisfactory plan of treatment

is to commence therapy of anxiety with meprobamate and to substitute pentylenetetrazol when the effect of meprobamate commences to lessen. The effectiveness of ataractic drugs in ambulatory patients may be entirely different from that in institutionalized geriatric patients. The impact of the drug must be considered in sociologic and economic terms as well as in physiologic and somatic alterations. Depression of the patterns of action necessary in an emergency, and a detached lack of responsibility caused by the unnecessary use of ataractic drugs, present sociologic dangers.

MARGINAL PEPTIC ULCER IN ELDERLY PATIENTS.

Stafford, C. E., and Hinshaw, D. B. *California Med.* **88:** 155 (Feb.) 1958.

Marginal peptic ulcer may follow gastric operation of any type and may appear in any age group. Old age affords no protection. With increasing frequency, elderly patients are having marginal ulceration or it is being noted more often. In a study of 22 patients, 65 years of age or over, with marginal ulcers, 19 of the ulcers were gastrojejunal and 3 gastroduodenal. The gastroduodenal ulcers followed pyloroplasty and vagotomy in 2 patients and a Billroth-I gastric resection in 1 patient. The 19 patients with gastrojejunal ulcer were aged 65 to 80 years. In 1 patient, ulcer symptoms commended at age 72. In 6 patients, the operation preceding the gastrojejunal ulcer was performed when they were over 65 years old. Sixteen of the 19 ulcers occurred after gastroenterostomy and 3 after Billroth-II partial gastrectomy. Gastro-enterostomy without vagotomy and minimal gastric resection do not afford adequate protection from subsequent marginal ulceration in the elderly. Abdominal pain and melena in a patient with a history of operation for peptic ulcer suggests the presence of marginal ulcer. When physical signs are minimal or x-ray evidence inconclusive, the diagnosis may be confirmed only at operation. Adequate (70 per cent) gastric resection yields the best results in treating stomal ulcers. When the patient is a poor surgical risk, vagotomy and pyloroplasty can be performed, but the greater danger of recurrence must be accepted. The complications in the series reported were similar to those in peptic ulcer in general—massive hemorrhage, severe pain, perforation, stomal obstruction and gastrojejunocolic fistula. Perforation and massive hemorrhage caused 3 deaths. The mortality rate, therefore, was comparable with that previously reported for complications of peptic ulcer in elderly patients.

CHLORPROMAZINE AND COMMUNICATION PROCESSES.

Tourlentes, T. T.; Hunsicker, A. L., and Hurd, D. E. *A.M.A. Arch. Neurol. & Psychiat.* **79:** 468 (Apr.) 1958.

Chlorpromazine was administered to 34 female chronic schizophrenic patients aged 45 to 72 years and an attempt made to evaluate its effect upon communcation processes by using psychologic tests, recorded psychiatric interviews, sociometric evaluations, and a cinematographic recording of spontaneous behavior. A dosage of 200 mg. was continued for a six-week period, preceded in one group and followed in a second group by placebo medication so that the results could be compared. The control group of 11 subjects received placebo for twelve weeks. The patients were evaluated before the experiment and after each six-week period. Statistical analysis of the test scores failed to show any significant changes as a result of chlorpromazine therapy. Some reduction in anxiety was observed. The reasons why chlorpromazine did not facilitate communication processes as measured here are discussed. The tests may not have detected subtle changes that occurred. The tests were confined to overlearned behavior patterns. The measurement of efficacy in learning novel tasks and in problem-solving activities might be a better approach.

AN EVALUATION OF FUNCTIONAL PSYCHOSES IN OLD AGE.

Williams, W. S., and Jaco, E. G. *Am. J. Psychiat.* **114:** 910 (Apr.) 1958.

A study of 2,248 psychotic patients more than 60 years of age showed that a larger percentage than would have been expected had functional psychotic reactions. The incidence

of functional disorders was markedly greater among patients in public mental hospitals than in patients in teaching and private hospitals. Other studies have indicated that social factors contribute to functional psychosis in old age. In this study, the incidence rates of functional psychosis for 3 ethnic groups (Anglo-American, Spanish-American, and Negro) were compared by rural versus urban status, and according to migrant status, marital status, and occupational class. The results furnished evidence of a close relationship between social factors and mental illness in later life. That ethnicity plays a role was indicated by a high incidence of mental illness among elderly Spanish-American females. That occupation played a part was indicated by a high incidence of functional psychoses among manual workers. This suggests that the change in status which occurs with aging is significant and that aging must be considered a social as well as a physical process. The reaction of an elderly person to an obsolescent dependent status with the loss of personal identity probably is a major source of pathologic behavior. The conclusion that a functional illness characterized by a depressed mood is as typical of mental illness after the age of 60 as is an illness characterized by a chronic brain syndrome, or even more so, seems to be warranted. In investigating psychiatric disorders in aging people, consideration should be given to the possibility of a functional form of senility in addition to more commonly recognized organic pathology.

ASSAULTIVE BEHAVIOR IN THE AGED.

Winkler, G. E., and Rosner, H. *New York J. Med.* **58:** 515 (Feb. 15) 1958.

Among 327 persons charged with felonious assault, manslaughter, homicide, or murder, who were admitted to the psychiatric prison ward of Kings County (New York) Hospital during a seven-year period, 47 (14 per cent) (according to the table presented) were 50 years of age or older. Chronic brain syndrome with arteriosclerosis was diagnosed in 21, 16 men and 2 women in this group being more than 60 years old. The other diagnoses were: character and behavior disorders, 14 (4 aged 60 or more), schizophrenic reactions, 3; and involutional melancholia, 9 (1 past the age of 60 years). The oldest patient was an 82-year-old woman. Only 9 patients in this elderly group showed a typical brain syndrome characterized by disorientation, confusion, memory defects, and high-grade intellectual deterioration. Emotional disturbances predominated in the other patients; these were classified as depressed and paranoid types of chronic brain syndrome associated with cerebral arteriosclerosis. Arteriosclerotic parkinsonism was present in 2 patients. Only 2 patients past the age of 60 had a history of previous arrest, and this for a minor offense. Since the majority of the patients had not deteriorated intellectually but were disturbed emotionally, it was sometimes difficult to establish a diagnosis of a commitable psychiatric disorder to give to the court examining these patients in order to arrive at their proper disposition. Observation showed that the degree of atrophy of the brain caused by cerebral arteriosclerosis or senile brain disease is not correlated directly with the degree of mental abnormality manifest clinically. This study highlights the interplay between social and emotional factors and ego impairment resulting from the brain process. Thus the early manifestations of organic brain disease are often emotional, and detected by the court rather than the physician. The concept of organic brain syndrome manifesting itself in severe intellectual disorganization is misleading. Neuropsychiatric mechanisms operative in assaultive behavior in the aged are discussed, with emphasis upon the tendency in elderly persons with organic brain disease toward an attitude of denial of illness and toward the development of catastrophic reactions upon being confronted by tasks they are unable to solve. The shunting reaction occurred in the 2 patients with arteriosclerotic parkinsonism—from a frustrated state of dependency, the patient suddenly reacted with a mechanism for denial of illness and was able to interrupt his rigidity and perform an assaultive act. When irreversible changes have occurred in a psychiatric patient who shows dangerous and assaultive trends, there is no alternative to referral to a psychiatric hospital. The relief of social pressures that often account for emotional disturbances in old age, lifting of feelings of responsibility, and the inspiration of a sense of group identification may help to prevent assaultive behavior.